Date: September 5, 2001

From: Ellis F. Unger, M.D., DCTDA, OTRR

Subject: Clinical Review of BLA 99-1492/ STN103951
Amgen, Inc.:
Darbepoetin alfa (ARANESP™) for the treatment of anemia associated with chronic renal failure.

Through: Marc Walton, M.D., Ph.D., Chief, General Medicine Branch, DCTDA
Karen Weiss, M.D., Director, DCTDA

To: BLA 99-1492/ STN103951 File

This document is the Medical ~~Officer Clinical Review for BLA-99-~~1492/ STN103951

Sponsor: Amgen, Inc.
Product: Darbepoetin alfa (ARANESP™)
Proposed Indication: Treatment of anemia associated with chronic renal failure

Material Reviewed – Dates of Submission:

Original Submission – December 28, 1999

Key Amendments:
Amendment 2 – May 30, 2000 – Excerpt of Annual Report: Safety in Ongoing Studies
Amendment 20 – December 28, 2000 – Responses to requests for information, post-marketing commitments and final clinical study reports for protocols 980202 and 980211
Amendment 26 – February 21, 2001 – Response to CBER Action Letter of February 16, 2001
Amendment 33 – May 15, 2001 – Corrected case report tabulations for Study 980211

Table of Contents

Abbreviations Used in This Review:

AE	adverse event
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate tranaminase
$AUC_{(0-\infty)}$	area under the serum concentration time curve from zero to infinity
BIW	twice weekly
BP	blood pressure
bpm	beats per minute
C_0	peak concentration at time zero
CAPD	chronic ambulatory peritoneal dialysis
CBC	complete blood count
CHO	Chinese hamster ovary
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CL	clearance
CLAS	Clinical Logistics Assay System
C_{max}	maximum observed concentration
cpm	counts per minute
CRA	clinical research associate
CrCL	creatinine clearance
CRF	chronic renal failure
CSMT	Clinical Studies Management Team
DBP	diastolic blood pressure
df	degrees of freedom
dL	deciliter
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbant assay
EPO	recombinant human erythropoietin (Epoetin alfa)
ESRD	end-stage renal disease
GCP	good clinical practice(s)
h	hour
Hb	hemoglobin
HCT	hematocrit

HD	hemodialysis
Hgb	hemoglobin
HIV	human immunodeficiency virus
HR	heart rate
HSA	human serum albumin
HTN	Hypertension
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IV	intravenous
IVRS	interactive voice response system
kg	kilogram
Kt/V	K = rate of urea clearance by artifical kidney; t = duration of dialysis; V = volume of distribution of urea
K-M	Kaplan-Meier
mg	microgram
MI	myocardial infarction
$MRT_{(0-\infty)}$	mean residence time to infinity
MSE	mean squared error
PD	peritoneal dialysis
PTH	parathyroid hormone
QOW	every other week
QW	weekly
r-HuEPO	recombinant human erythropoietin
ROR	rate of raise
SAE	serious adverse event
SC	subcutaneous
TIA	transient ischemic attack
TIW	three times weekly
T_{max}	time at which C_{max} occurs
TVA	thrombosis vascular access
URR	urea reduction ratio
V_0	initial volume of distribution
V_{ss}	volume of distribution at steady-state
VS	vital signs

Proposed ARANESP Indication:

The proposed ARANESP indication is: "ARANESP™ is indicated for the treatment of anemia associated with chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis. Treatment of anemia of CKD has been associated with a reduction in red blood cell transfusions."

Background:

Erythropoietin is a glycoprotein produced in the kidney in response to hypoxemia that stimulates division and differentiation of committed erythroid progenitors in the bone marrow, leading to red

blood cell production. With the destruction of renal parenchyma associated with CRF, production of erythropoietin is reduced, causing normochromic, normocytic anemia.

Licensed Products for the Treatment of Anemia of CRF:

Epoetin alfa (EPO), manufactured by Amgen, Inc., was approved in the U.S. in 1989 for treatment of anemia associated with CRF. Subsequently, its indications were expanded to include anemia in zidovudine-treated HIV-infected patients, anemia in cancer patients receiving chemotherapy, and anemia in patients scheduled to undergo elective, non-cardiac, non-vascular surgery.

Pursuant to a patent licensing agreement between Amgen and Ortho Biotech (a subsidiary of Johnson & Johnson), Amgen retained the exclusive rights to market EPO for use in CRF patients in the U.S. (under the trade name "Epogen®"), and Ortho Biotech retained the rights to market the product for non-dialysis use in the U.S. under the trade name "Procrit," though the product is manufactured by Amgen. Ortho (Johnson & Johnson) retains marketing rights for distribution and sale of EPO outside the U.S., and manufactures the product independently of Amgen. Epoetin beta, a related product, is marketed outside the U.S. for treatment of anemia associated with CRF under the trade name Recormon.

The CRF indication statements for EPOGEN® and PROCRIT are identical:

> ***Treatment of Anemia of Chronic Renal Failure Patients***
> EPOGEN® / PROCRIT is indicated for the treatment of anemia associated with CRF, including patients on dialysis (ESRD) and patients not on dialysis. EPOGEN® /PROCRIT is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or Hgb determinations) and to decrease the need for transfusions in these patients.

ARANESP Product:

ARANESP differs from erythropoietin by the incorporation of 5 amino acid changes in the primary sequence. These alterations create 2 additional consensus N-linked carbohydrate addition sites. ARANESP has 5 N-linked carbohydrate moieties, whereas endogenous erythropoietin and EPO have 3. The extra glycosylation sites are thought to account for the longer half-life of AREANESP relative to EPO (2- to 3-fold longer circulating half-life when administered IV or SC, according to the sponsor). The sponsor's premise is that ARANESP may be administered less frequently than EPO, because of the longer half-life.

Scope of this Review:

The ARANESP clinical development program was comprised of 13 studies and included 2198 subjects with chronic renal failure (CRF), of whom 1598 received ARANESP and 600 received EPO as an active comparator. All studies have been funded by Amgen, Inc.

Clinical studies submitted in support of this marketing application can be broadly divided into 4 categories:

- pharmacokinetic analyses of ARANESP in CRF subjects and healthy volunteers (Studies 960224, 970235, 980194, 980212, 990134)

- correction of anemia in CRF subjects not previously receiving EPO (Studies 960245, 960246, 980202, 980211)
- maintenance of erythropoiesis in CRF subjects who had been previously maintained on EPO (Studies 970200, 980117, 980140)
- continuation of ARANESP in subjects who completed 52 weeks of treatment under another investigation (Study 980160)

The individual studies are summarized in this review, followed by an integrated summary of safety. Investigations with similar designs and objectives (Studies 980211 and 980202; Studies 970200 and 980117) are reviewed together. Study 980194 was a pharmacokinetic study, conducted in a subset of 16 subjects enrolled in study 980140, and is discussed under the latter study.

Pharmacokinetic Studies:

Protocol 960224:

Title: A Comparison of the Pharmacokinetics of ARANESP and Epoetin alfa in Patients With Chronic Renal Failure Receiving Dialysis
Study Period: December, 1996 – April, 1997
Center: Single-center; King's College Hospital, London, UK

The study represented the initial introduction of ARANESP into humans, and was performed in the United Kingdom, prior to the filing of the IND.

Objectives:

The primary objectives of this study were to investigate the pharmacokinetics of single-dose IV ARANESP (0.5 μg/kg) and Epoetin alfa in subjects with chronic renal failure (CRF) receiving dialysis. The safety profile of ARANESP was also evaluated in this setting.

Design:

This was a single center, randomized, double-blind, two-period, two-treatment crossover study in medically-stable subjects with CRF undergoing PD. Subjects were to be randomized to a single IV bolus of ARANESP (0.5 μg/kg) or Epoetin alfa (100 U/kg). Following a 28 day washout period, subjects were to cross-over to the alternate study agent. These treatments were followed by an optional open-label single SC dose of ARANESP (0.5 μg/kg).

Study Population:

The study population was to include clinically stable adults with ESRD receiving PD, with hemoglobin (Hgb) ≥ 9 g/dL, body mass index (BMI) 17 – 30, and no Epoetin alfa therapy within 3 months prior to enrollment in the study.

Endpoints:

Principal pharmacokinetic endpoints evaluated included area under the serum concentration-time curve (AUC), terminal elimination half-life ($t_{½,z}$) and volume of distribution in the central compartment (V_c).

Results:

Patient Enrollment, Treatment Assignment and Compliance:

Initially, 10 subjects were randomized into the study. One subject with a serious adverse event (SAE), (peritonitis) withdrew after receiving IV ARANESP in period 1, and was replaced. Thus, a total of 11 subjects were enrolled in the study. The median age was 58 years (range 27 – 75), median baseline Hgb was 10.4 g/dL (range 9.1 – 12.2). Seven (64%) of the subjects were male. Six subjects received SC ARANESP in period 3. One subject violated inclusion criteria with BMI > 30.

Pharmacokinetic Results:

The profiles for ARANESP and EPO administered IV were described by linear compartmental models with first order elimination. The volume of distribution was approximately equivalent to plasma volume, and similar to that of EPO. The terminal elimination half-life for ARANESP was 25.3 ± 2.2 hours, approximately 3-times that of EPO (8.5 ± 2.4 hours). Clearance from the central compartment was 1.6 ± 0.3 mL/h/kg, ~40% that of EPO. The $AUC_{(0-\infty)}$ for ARANESP was 291 ng•h/mL, or ~220% that of EPO. The sponsor found no evidence of a time-by-treatment interaction or period effect for any of the pharmacokinetic parameters studied.

A subset of 6 patients consented to be re-treated with ARANESP by the SC route (open label). Serum levels of ARANESP increased slowly after SC administration, reaching a peak at a mean of approximately 54 hours. Bioavailability was ~37% for the SC route. The terminal half life was ~49 hours, or approximately double that of IV ARANESP, suggesting that absorption is rate-limiting for the SC route. The mean $AUC_{(0-\infty)}$ was 108 ng•h/mL, and was 33% that of IV ARANESP.

Safety:

There were no deaths of apparent allergic reactions. Nine subjects reported AEs; none appeared to be related to study drug.

Summary for Protocol 960224:

This study constituted the initial introduction of ARANESP in humans. Single-dose IV and SC ARANESP were well-tolerated. The pharmacokinetic data demonstrated a terminal elimination half-life of NESP approximately 3-fold longer than that of EPO. For SC administration of ARANESP, the mean half-life was approximately twice that of IV ARANESP, and absorption was rate-limiting.

Protocol 970235:

Title:	A Randomized, Pharmacokinetic Study of ARANESP and Recombinant Human Erythropoietin (EPO) Administered by Intravenous Bolus in Patients With End-Stage Renal Disease Receiving Hemodialysis
Study Period:	January, 1998 – ongoing. Enrollment is complete, and the data relevant to the primary study endpoint were submitted with an interim cutoff date of June 29, 1999. Extended follow-up is ongoing.
Centers:	Five (5) centers in the U.S.

This study protocol was submitted in November, 1997 as the initial ARANESP study to be conducted under IND (IND -----).

Objectives:

The primary study objective (completed) was to assess the pharmacokinetics of ARANESP and EPO following multiple IV administrations in subjects with ESRD receiving HD. Secondary objectives are to assess the safety profile of ARANESP, and to determine the dose and schedule of ARANESP required to maintain a steady state of Hgb.

Design:

This is a multicenter, phase 1/2, randomized, open-label pharmacokinetic study. After an initial screening/baseline period, subjects with CRF maintained on HD receiving EPO therapy on a stable and ongoing basis were to be randomized to one of three study groups: 1) TIW EPO (no change in regimen); 2) TIW ARANESP; or 3) QW ARANESP. Randomization was stratified by center. All agents were to be administered by the IV route. Doses of ARANESP or EPO were to be adjusted to maintain the Hgb within a target range of 9 -13 g/dL, while not allowing a change from baseline beyond 1 g/dL below to 1.5 g/dL above their baseline. Pharmacokinetic sampling was to be performed on day 1, week 12, and at Hgb steady-state or between weeks 36 and 40, whichever occurred first. Subjects could continue treatment for up to 52 weeks.

Calculation of the starting ARANESP dose was based on the prior maintenance EPO dose. Accumulation of ARANESP was a potential concern with the TIW dosing schedule, thus the conversion factor was more conservative for TIW versus QW ARANESP dosing:

- Subjects randomized to QW ARANESP received an initial total weekly ARANESP dose based on the proportionality 600 U EPO/kg/week → 1 μg ARANESP/kg/week.

- Subjects randomized to TIW ARANESP received an initial total weekly ARANESP dose based on the proportionality 1000 U EPO/kg/week → 1 μg ARANESP/kg /week, to be administered in 3 divided doses.

Complete blood count was assessed twice weekly through week 4, then weekly through week 12. For weeks 13 – 52, Hgb was evaluated weekly, but monitoring was to be decreased to QOW once a Hgb steady-state was reached.

Study Population:

The study population was to include adult subjects with CRF receiving HD for ≥ 3 months, clinically stable, Hgb 9.5 to 12.5 g/dL, without evidence of iron deficiency (transferrin saturation ≥ 20%), and on stable EPO therapy on a TIW schedule for ≥ 2 months.

Endpoints:

Primary pharmacokinetic endpoints included: clearance from the central compartment, volume of distribution at steady state (V_{ss}), terminal half-life ($t_{½,z}$) and area under serum concentration-time curve ($AUC_{(0-\infty)}$). PK endpoints were assessed at day 1, week 12, and at Hgb steady-state, or between weeks 36 and 40, whichever occurred earlier.

Secondary endpoints included the incidence of adverse events (AEs), AE occurrence rates, and the dose of ARANESP required to maintain Hgb within the target range.

Pharmacokinetic Sampling:

For each sampling period, sera were to be collected pre-dose, at 5 and 30 minutes, and at 1, 2, 5, 24, 30, and 48 hours. Additional samples were collected in the QW ARANESP group at 72 and 96 hours. ---------- were utilized to assess ARANESP and EPO serum levels.

Results:

Patient Enrollment, Treatment Assignment and Compliance:

The first subject was enrolled January 19, 1998. A total of 47 subjects, enrolled at 4 sites, were randomized into the 3 treatment groups: 15 subjects were assigned to EPO, 15 to TIW ARANESP, and 17 to QW ARANESP. All randomized subjects received study drug. At the time of data cutoff for this analysis, 22 subjects (47%) had completed the study (i.e., had completed the steady-state pharmacokinetic analyses), 14 (30%) had been discontinued from the study and 11 (23%) were still on-study. Reasons for prematurely discontinuing the study included AEs (4 subjects), death (4 subjects), administrative decisions (3 subjects), subject request (2 subjects), and renal transplant (1 subject).

Table 1: Subject Disposition - Study 970235

	EPO TIW	ARANESP TIW	ARANESP QW
	n = 15	n = 15	n = 17
Total Completed	9 (60%)	6 (40%)	7 (41%)
Total Discontinued	3 (20%)	5 (33%)	6 (35%)
Intolerable Adverse Event	1 (7%)	2 (13%)	1 (6%)
Withdrawal Requested	0 (0%)	1 (7%)	1 (6%)
Administrative Decision	1 (7%)	0 (0%	2 (12%)
Death on Study	1 (7%)	2 (13%)	1 (6%)
Kidney Transplant	0 (0%)	0 (0%)	1 (6%)
Total Ongoing	3 (20%)	4 (27%)	4 (24%)

Protocol deviations were reported in 45 of 47 subjects. Deviations involving study agent dosing were reported in 11 subjects, including ≥1 missed dose before a PK sampling period (7 subjects), incorrect dose and/or dose adjustment not in accord with protocol (7 subjects), >10% of planned doses missed (3 subjects), and incorrect route of administration (1 subject). Five (5) subjects randomized to ARANESP received a dose of EPO. Eight (8) subjects received RBC transfusions before reaching Hgb steady state.

Demographic Characteristics and Baseline Disease Status:

For the study as a whole, 66% of the subjects were male. Forty-nine percent (49%) of subjects were Caucasian, with 36%, 11% and 4% of African, Hispanic and Asian descent, respectively. Median age was 53 years; 40% of subjects were age 65 or older, and 13% were age 75 or older. Median Hgb was 11.0 g/dL (range 9.9 – 12.3 g/dL). Median transferrin saturation was 29% (range 20 – 59%), indicating that the population as a whole was not iron deficient. Leading causes of renal failure were diabetes (32%) and hypertension (23%). Baseline EPO doses were similar in the three groups. The median baseline EPO dose was 113 U/kg/week. Demographic

characteristics and baseline disease status were reasonably balanced between groups, with the exceptions of gender (males comprised 80% of the EPO group and 59% of the ARANESP groups) and time since onset of renal failure (median 55 months in the EPO group; ~24 months in the ARANESP groups).

Pharmacokinetic Results:

For a detailed summary of pharmacokinetic results, see the Clinical Pharmacology and Toxicology Review document.

Efficacy:

Median doses of ARANESP required to maintain Hgb at steady state were 62 μg/week for the TIW group and 43 μg/week for the QW group. The sponsor analyzed all randomized subjects who received ≥ 1 dose of study agent and provided a baseline and ≥ 1 post-baseline value. Achievement of a Hgb value in the target range was observed in 87% of subjects in the EPO group, 60% of subjects in the TIW ARANESP group, and 76% of subjects in the QW ARANESP group. The sponsor interpreted the lower success rates in the ARANESP groups as a reflection of the lower initial study drug doses in these groups. In support of this hypothesis, initial ARANESP doses were increased by a mean of 5-fold in the TIW ARANESP group, and 3-fold in the QW ARANESP group, but by only 1.4-fold in the EPO group.

There were no important differences between treatment groups with respect to steady-state hematologic parameters (Hgb, hematocrit [HCT], and reticulocyte counts).

Safety:

The median duration of exposure was 48 weeks for both ARANESP treatment groups and 52 weeks for the EPO group. Thirty-one (31) of 32 subjects in the ARANESP groups and all subjects in the EPO group experienced AEs. Adverse events were typical for this patient population, with no apparent differences between the treatment groups. Serious adverse events were reported in 20 of 32 ARANESP-treated subjects (63%) and 7 of 15 EPO-treated subjects (47%). Pneumonia, septic shock and gangrene were reported in 13% of EPO-treated subjects and none of the ARANESP-treated subjects. Otherwise, SAEs were similar in incidence rates between treatment groups. Two subjects developed a malignancy on study: an ARANESP subject developed malignant lymphoma and an EPO subject developed renal carcinoma. There were no apparent shifts in vitals signs or laboratory parameters in the either the ARANESP or EPO groups; however, there was considerable inter-and intra-subject variability in some parameters. No signs or symptoms of allergic reactions to ARANESP or EPO were reported.

Reviewer's Comments: Given the small number of subjects enrolled in this study and the high background rate of AEs in the CRF patient population, these data are limited in their informativeness. The safety results of this study will be addressed further as part of CBER's integrated analysis of safety.

Deaths

Six deaths occurred on-study: 4 in the combined ARANESP groups (incidence = 13%) and 2 in the EPO group (incidence = 13%). There were 2 sudden deaths in the ARANESP-treated subjects. Both occurred in elderly (67 and 72 year-old) diabetic males. The other deaths in ARANESP-treated subjects included: 1) sepsis with aspiration pneumonia and 2) cerebrovascular

accident, increasing hypertension (HTN) with subsequent voluntary termination of dialysis. In the EPO group, the deaths were attributable to 1) gram negative sepsis, and 2) asthmatic bronchitis, fluid overload, and pneumonia in a 35 year-old male with a history of ischemic heart disease and asthma.

Reviewer's Comments: In general, deaths appeared to be related to coexisting illnesses including diabetes, coronary artery disease, and peripheral vascular disease. The deaths from cerebrovascular accident with increasing HTN, and the death related to "asthma" with fluid overload could be related to the effects of the study agents. The safety results of this study will be addressed further as part of CBER's integrated analysis of safety.

Withdrawals Due to Adverse Events
There were 3 withdrawals in ARANESP-treated subjects for AEs: these events included pulmonary edema, dyspnea, and cerebrovascular disorder. There was one withdrawal in the EPO group for septic shock.

Antibody Assays
The median duration for antibody monitoring was ~50 weeks for ARANESP-treated subjects. All assays were negative.

Summary for Protocol 970235:

The results of interim analyses from this multicenter, randomized, open-label, phase 1/2 study show that the terminal half-life for ARANESP is longer than that of EPO. Percentages of subjects achieving Hgb steady-state were, by group, 87%, 60%, and 76% for EPO, TIW ARANESP, and QW ARANESP, respectively. Median ARANESP doses required to maintain Hgb within a range of 9 – 13 g/dL were 62 μg/week for the TIW group and 43 μg/week for the QW group. These data are of limited strength with respect to safety, given the small sample sizes and the high background frequency of AEs in the CRF patient population.

Protocol 980212:

Title:	An Open-Label, Randomized, Crossover Study to Determine the Pharmacokinetics of ARANESP in Pediatric Patients with Chronic Renal Failure (CRF) or End-Stage Renal Disease (ESRD)
Study Period:	April, 1999 – ongoing; interim analysis as of August 18, 1999
Centers:	Five (5) centers in the US
Subjects:	9 randomized

This study is being conducted under IND --------. Enrollment was incomplete at the time of interim analyses, and remains incomplete.

Objectives:

The objective is to determine the pharmacokinetics of single-dose IV and single-dose SC ARANESP in pediatric subjects with CRF (receiving or not receiving dialysis). The secondary objective is to investigate the safety profile of ARANESP in the pediatric population.

Design:

This is an ongoing, multicenter, open-label, 2-period, 2-treatment, crossover study. After a screening period (which included a 7-day washout period for subjects receiving EPO before the study), pediatric subjects with CRF were to be randomized to receive a single injection of ARANESP at a dose of 0.5 μg/kg by the IV or SC route. Randomization was to be stratified by age (1–6, 7–11, 12–16), and constrained such that each age category would be limited to 6 subjects. Sera were to be collected before and at predefined time points after ARANESP administration (up to 168 hours) to evaluate ARANESP pharmacokinetics and bioavailability. After a 14–16 day washout period, ARANESP was to be readministered at the same dose, via the alternate route. Blood samples were to be collected to assess ARANESP pharmacokinetics through 168 hours. An end-of-study evaluation was planned after a final 7-day washout period. Laboratory variables (i.e., hematology, biochemistry, and iron status) were to be assessed by local laboratories; ARANESP pharmacokinetic analyses and antibody assays were to be performed at Amgen.

The ARANESP assay is a ----------. Endogenous erythropoietin and EPO cross-react with the assay. Thus, ARANESP serum concentrations are to be baseline-corrected by direct subtraction. This method assumes that the non-NESP contribution to the serum concentration remains constant over time. The primary pharmacokinetic analysis is to be performed using non-compartmental methods, with compartmental modeling as a secondary analysis. Serum samples for detection of anti-NESP antibodies are to be obtained before the initial ARANESP dose, on study day 15, and at end of study. Antibodies are to be detected using a ---------- screening assay, and a ---------- is being used for detection of neutralizing antibodies.

An interim analysis was scheduled to be performed on data collected through 8/18/99 to support the ARANESP market application, with no intention of stopping the trial early and no planned confidence interval adjustments as a result of these analyses.

Study Population:

Inclusion criteria were designed to select pediatric subjects (age 1–16), weight ≥ 9 kg, with CRF (estimated GFR < 30 mL/min/1.73 m^2) or ESRD receiving dialysis, with baseline Hgb ≥ 9 g/dL and no evidence of iron deficiency (serum transferrin saturation ≥ 20%). Major exclusion criteria include uncontrolled HTN, recent grand mal seizures or major surgery, hepatic disease, and malignancy.

Study Endpoints:

Primary:

The primary endpoint is the terminal half-life of ARANESP after IV or SC injection.

Secondary:

IV dosing: peak concentration at time zero (C_0), area under the serum concentration time curve from zero to infinity ($AUC_{(0-\infty)}$), mean residence time to infinity ($MRT_{(0-\infty)}$), clearance (CL) and initial volume of distribution (V_0)
SC dosing: maximum observed concentration (C_{max}), the time at which C_{max} occurs (T_{max}), absorption rate, bioavailability, $AUC_{(0-\infty)}$, $MRT_{(0-\infty)}$, and relative clearance.

Safety:

Safety endpoints include incidences of AEs, vital signs, hematology values, electrolytes, phosphorous, ALT, AST, alkaline phosphatase, glucose, urea, serum creatinine, total bilirubin, albumin, uric acid, transferrin saturation, and ARANESP antibody formation.

Study Amendments:

The study was amended once on 6/21/99 to add an interim analysis on data collected through 8/18/99 in support of the ARANESP market application, to adjust several time points to reduce the number of blood draws, and to decrease the minimum age of subjects from 2 to 1, for the purpose of increasing enrollment.

Interim Results:

Enrollment and Disposition of Subjects:

Seventy-nine (79) subjects were screened; 9 subjects were enrolled and included in the interim analyses. Eight of the 9 subjects received ARANESP (one subject was found to violate inclusion criteria for GFR and not treated). Subject recruitment was ongoing at the time of interim analysis. One subject completed the first period (IV), but not the second period (SC). One subject received a single dose of EPO 4 days before SC ARANESP dosing in the first period and another EPO 3 days after SC ARANESP. Thus, the SC pharmacokinetic profile was not evaluable.

Baseline Characteristics:

Five males and 4 females were enrolled, with a median of 14 years (range: 7–16 years) and a median mass of 41.5 kg. No subjects were in the 1- to 6-year-old age group, 2 subjects were in the 7- to 11-year-old age group (one was 7 years old ; one was 10 years old), and 7 subjects were in the 12- to 16-year-old age group (the youngest of these subjects was 13). For the study overall, median baseline Hgb was 11.6 g/dL (range 9.1–13.4 g/dL). Six subjects were receiving HD; 3 were not receiving dialysis.

Pharmacokinetics:

After IV administration, ARANESP serum concentrations declined in a biphasic fashion. The volume of distribution was similar to that of adults, and suggested that ARANESP is distributed primarily to the intravascular space. After SC dosing, ARANESP appears to be absorbed slowly, at a rate that determines the terminal phase of the time-concentration profile.

Reviewer's Comments: As noted above, only 2 subjects (aged 7 and 10) were under the age of 13. For the pharmacokinetic analyses, the 10 year-old contributed no data whatsoever (samples were insufficient on day 1; samples on Day 15 were not obtained in time for this interim analysis). The 7 year-old contributed no data for SC ARANESP administration, because an EPO dose had been inadvertently administered between 72 and 96 hours before SC ARANESP. Thus, for subjects under the age of 13, pharmacokinetic data were obtained for a single IV ARANESP injection in a single subject. These data are not adequate in their generalizability to a pediatric population, and are not adequate to support pediatric labeling.

Safety Results:

During this study, 6 of the 8 subjects (75%) who received ARANESP reported 1 or more AEs. No deaths, SAEs, or AEs leading to withdrawal were reported. No notable differences in the type and frequency of AEs or trends in hematology or chemistry variables were apparent by treatment sequence or route. Mean blood pressure and mean heart rate were stable throughout the study. Antibody assays were reported for 8 subjects, but only 6 of these subjects had assay results reported after both ARANESP doses.

Reviewer's Comment: In light of a study design that involves administration of only 2 doses of ARANESP, and given the limited numbers of subjects studies to date, these data do not provide adequate support for the safety of ARANESP in the pediatric patient population.

Summary for Protocol 980212:

Based on very limited interim data, the pharmacokinetics of ARANESP in older pediatric subjects may be similar to that of adults. Safety in the pediatric population can not be reliably assessed on the basis of these data. The interim data from this study are not adequate to serve as a basis for pediatric labeling.

Protocol 990134:

Title:	A Double-Blind, Randomized, Crossover Study to Compare the Pharmacokinetics and Safety of Subcutaneously Administered Single Doses of Two Formulations of Novel Erythropoiesis Stimulating Protein (NESP) in Healthy Subjects
Study Period:	May 19, 1999 – August 10, 1999
Centers:	One (1) center in Freiburg, Germany
Subjects:	28 randomized

This study was conducted under IND 7413.

Objectives:

To compare the pharmacokinetics and safety profiles of two formulations of ARANESP (formulated with and without human serum albumin [HSA]), both administered as single 1 μg/kg SC injections in healthy adults. The HSA-free (HSA-) formulation contains polysorbate 80 in lieu of HSA.

Design:

This was a single-center, double-blind, randomized, 2-period, 2-treatment, crossover study in healthy non-obese subjects. After a 14-day screening period, fasting subjects received a single injection of ARANESP 1.0 μg/kg SC, as either the HSA+ or HSA- formulation, injected into the thigh. Sera were collected before, and at pre-defined time points after, ARANESP administration (up to 14 days) to evaluate ARANESP pharmacokinetics and bioavailability. After a 42-day washout period, the alternate formulation of ARANESP was administered, such that each subject served as his/her own control. An end-of-study evaluation was conducted 14 days after the second injection. Both ARANESP formulations were provided in ~1 mL vials at a concentration of 100 μg/mL. ARANESP pharmacokinetic analyses and antibody assays were performed at Amgen. ARANESP was assayed using a ----------
---

Endogenous erythropoietin and EPO cross-react with the assay. Thus, ARANESP serum concentrations were baseline-corrected by direct subtraction. Serum samples for detection anti-NESP antibodies were obtained before the initial ARANESP dose, and on day 42 and 57. A ----------screening assay was used to detect immunoreactivity to ARANESP, and a ---------- bioassay was used to detect neutralizing antibodies.

Study Population:

Inclusion criteria were designed to select healthy adult subjects (age 18–65), with weight within ±20% of ideal body weight.

Study Endpoints:

Primary:

The primary study endpoint was area under the serum concentration-time curve from time 0 to the time of the last quantifiable concentration ($AUC_{(0-t)}$).

Secondary:

Secondary endpoints included maximum observed concentration (C_{max})?time-to-maximum observed-serum concentration (T_{max}), and area under the serum concentration time curve from zero to infinity ($AUC_{(0-\infty)}$).

Safety:

Safety parameters included the incidences of AEs, vital signs, hematology and biochemistry values, ECG changes, and ARANESP antibody formation

Results:

Enrollment and Disposition of Subjects:

Forty-nine (49) subjects were screened; 28 subjects were enrolled (14 per treatment sequence), and all completed the study.

Baseline Characteristics:

Fifteen males and 13 females were enrolled, with a median age of 31 years (range: 18–55 years) and a median mass of 70.0 kg. The mean Hgb levels, iron parameters, vital signs, platelet counts, and WBC counts were similar at baseline for the 2 treatment-sequence groups.

Pharmacokinetics:

After ARANESP administration, serum ARANESP concentrations increased slowly, reaching peak concentrations between 12 and 48 hours post-dose (median, 36 hours). Concentrations declined thereafter, generally in a monophasic manner; however, a second phase was observed for several subjects, with quantifiable concentrations generally up to 14 days post-dose. For each individual subject, the baseline-corrected concentration-time profiles for the 2 formulations were similar. Mean ARANESP concentration-time profiles for the 2 formulations were virtually superimposable. Mean values of $AUC_{(0-t)}$, C_{max}, and $AUC_{(0-\infty)}$ were very similar for the HSA+ and HSA- formulations. The ratios (HSA-/HSA+) for untransformed $AUC_{(0-t)}$, Cmax, and $AUC_{(0-\infty)}$ were 1.02 (90% confidence interval [CI]: 0.96, 1.09), 1.03 (90% CI: 0.95, 1.12), and 1.02 (90% CI: 0.95,

1.08), respectively. Parameter values and HSA-/HSA+ ratios obtained using transformed parameters were very similar to those obtained using the untransformed parameters.

Safety Results:

Fifteen (15) subjects reported AEs (54%), with events in 9 subjects classified by the investigator as treatment-related. Two (2) subjects reported 6 events characterized as severe (headache, nausea and/or vomiting), and 5 of these events were considered treatment-related (3 HSA+; 2 HSA-). None of the AEs was classified as serious. The only events reported in >1 subject were headache, hematoma, nausea and vomiting. No trends suggestive of a treatment-related effect were identified for any laboratory parameters. Anti-ARANESP antibodies were not detected for any subject during the study.

Reviewer's Comment: Given the lack of a placebo control group, the significance of subjective AEs is unclear.

Summary for Protocol 990134:

The pharmacokinetics of the HSA+ and HSA- formulations appear to be similar. The safety data do not raise any particular concerns with reference to the polysorbate formulation, although the strength of the data is limited given the limited sample size, and the single-dose, uncontrolled, study design.

Phase 2 Dose-Finding and Dose-Scheduling Studies:

Protocol 960245:

Title:	Dose-Finding and Dose-Scheduling Study of ARANESP Administered by Intravenous Bolus in Patients With Chronic Renal Failure Receiving Hemodialysis
Study Period:	February 1997 – ongoing; interim analysis as of 4/28/99
Centers:	Twelve (12) centers in the UK, Ireland, France and Canada
Subjects:	75 randomized

This study was not conducted under IND. Data on the primary study endpoints were included with the submission of the BLA; accrual of extended safety data is ongoing.

Objectives:

The objective was to determine the optimum dose and schedule of IV bolus ARANESP for treatment of anemia in subjects with CRF receiving HD, and to assess the safety of ARANESP in this setting.

Design:

This is an uncontrolled, multicenter, dose-escalation study to evaluate ARANESP at various doses and dose schedules. ARANESP was planned to be administered for an initial 4 week period (Part A), extending to 16 weeks (Part B) in subjects who attained an optimal Hgb response in Part A (i.e., Hgb rate of rise [ROR] of ≥ 1g/dL and < 3 g/dL), and then up to 52 weeks in subjects who agreed to continue with maintenance treatment. ARANESP was to be administered IV QW at doses of 0.075, 0.225, 0.45, 0.75, 1.5 and 4.5 μg/kg/dose; or administered IV TIW at doses of 0.025, 0.075, 0.15, 0.25, 0.5 and 1.5 μg/kg/dose.

Study Population:

Adult subjects with CRF and anemia, receiving hemodialysis (HD), clinically stable, Hgb < 10.0 g/dL, no EPO therapy within 3 months before the planned first dose of ARANESP.

Study Endpoints:

Primary:

Part A: Hgb rate of rise (ROR) over initial 4 weeks of treatment
Part B: Hgb level after 16 weeks of treatment

Secondary:

Part A: Change in hematocrit, RBC count, and reticulocyte count over the initial 4 weeks of treatment
Part B: Hematocrit, RBC count, and reticulocyte count after 16 weeks of treatment
Maintenance Period: Hgb, hematocrit, RBC count, and reticulocyte count
Safety: Clinical laboratory findings (hematology, coagulation, iron status, biochemistry), vital signs and treatment exposure

Safety:

Safety outcomes are to include the nature, frequency, severity, and relation to treatment of all AEs.

Results:

Seventy-five (75) subjects were randomized into the study, 72 of whom received study drug. This interim analysis was carried out when all subjects had been enrolled and completed 4 weeks of treatment in Part A, allowing analysis of the primary study endpoint. The median baseline Hgb concentration was 8.4 g/dL (range 5.2 – 10.6 g/dL) across all treatment groups. The dose-escalation phase of the study progressed to the 0.75-μg/kg/wk dose, and, in accordance with the recommendations of the Safety Monitoring Committee (SMC), all subsequent subjects were enrolled into this dose level unless they had an inadequate Hgb response, in which case they were eligible for re-entry at the 1.5 μg/kg/wk dose level. In total, there were 85 subject exposures among 72 unique subjects: 4 subject exposures at the 0.075 μg/kg/wk dose, 8 at the 0.225 μg/kg/wk dose, 10 at the 0.45 μg/kg/wk dose, 56 at the 0.75 μg/kg/wk dose, and 7 at the 1.5 μg/kg/wk dose.

Efficacy Results:

Part A: The results showed that there was a significant dose-related effect of ARANESP on the Hgb ROR, hematocrit, and RBC count, with no evidence of an effect on reticulocyte count over the initial 4 weeks of ARANESP dosing. The mean Hgb ROR over the initial 4 weeks was 0.01 g/dL (95% CI: -1.13, 1.16) for the 0.075 μg/kg/wk cohort, 1.19 g/dL (95% CI: 0.38, 2.00) for the 0.225 μg/kg/wk cohort, 1.27 g/dL (95% CI: 0.55, 2.00) for the 0.45 μg/kg/wk cohort, and 1.71 g/dL (95% CI: 1.41, 2.02) for the 0.75 μg/kg/wk cohort. There was no evidence of a schedule effect, and no evidence that the dose effect differed between schedules.

Part B: For the 51 subjects who responded to ARANESP in Part A and continued treatment, no significant differences were observed in either dose or schedule for Hgb, hematocrit, RBC counts, or reticulocyte counts after 16 weeks of dosing.

Maintenance Period: For the 32 subjects who continued dosing into the Maintenance Period, the mean Hgb was maintained between 10 - 13 g/dL from a mean baseline value of 8.36 g/dL. The mean hematocrit, RBC count, and reticulocyte count were also stable.

Safety Results:

The overall safety data for this study were broadly comparable to those expected for a population of CRF subjects undergoing HD. There were no study withdrawals, dose reductions, or withheld doses due to AEs. Antibody formation was not observed for any subject on study. No changes in laboratory variables, vital signs, or concomitant medications were observed that were considered to be clinically significant or related to study agent. There were 2 deaths on study. AEs and SAEs of this ongoing, uncontrolled study will be reviewed in CBER's integrated analysis of safety.

Pharmacokinetics:

There was a trend of increasing trough concentrations with increasing ARANESP dose. Wherein similar doses were administered either once or thrice weekly, the mean serum concentration was greater for the more frequent dose schedule.

Summary for Protocol 960245:

The interim analysis of this dose-escalation study suggests that ARANESP administered IV QW or TIW supports erythropoiesis in subjects with CRF receiving HD. No safety issues were apparent, though the study was not designed to adequately assess safety. There was a dose-related effect of ARANESP on the Hgb ROR over the initial 4 weeks of treatment. Doses of 0.225, 0.45, and 0.75 μg/kg/wk produced a Hgb ROR of $\geq$ 1 g/dL and < 3 g/dL over the initial 4 weeks (i.e., 0.25 to 0.75 g/dL/week). There was no apparent difference in Hgb response with ARANESP administered once versus 3 times weekly.

Protocol 960246:

Title:	A Dose-Finding and Dose-Scheduling Study of ARANESP Administered by Subcutaneous Injection in Patients With Chronic Renal Failure Receiving Peritoneal Dialysis
Study Period:	January 1997 – ongoing; interim analysis as of May 28, 1999
Centers:	Nine (9) centers in the UK, Ireland and Canada
Subjects:	66 randomized

This study was not conducted under IND.

Objectives:

The study objectives were to investigate the optimum dose and schedule of ARANESP for treatment of anemia when administered by SC injection in subjects with CRF receiving PD, to compare the ability of ARANESP and EPO to increase and maintain Hgb levels, and to investigate the safety profile of ARANESP in this setting.

Design:

This is an ongoing multicenter, open-label, dose-escalation study designed to evaluate ARANESP administered by the SC route at various doses and dose schedules. ARANESP was to be administered for an initial 4 week period (Part A), to be extended to 16 weeks (Part B) in subjects who attained an optimal Hgb response in Part A (i.e., Hgb rate of rise [ROR] of ≥ 1 g/dL and < 3 g/dL per 4 weeks), and then up to 52 weeks in subjects who agreed to continue maintenance treatment. ARANESP was to be administered SC QW at doses of ranging from 0.075 to 4.5 μg/kg/dose; or administered SC TIW at doses ranging from 0.025 to 1.5 μg/kg/dose.

The protocol was amended to add an EPO control arm to compare the ability of ARANESP and EPO to increase and maintain Hgb levels. For this sub-investigation, ARANESP was administered at a fixed dose of 0.45 μg/kg/wk QW. EPO was administered at a dose of 100 U/kg/wk BIW for ≤ 16 weeks. Both agents were administered by the SC route.

Study Population:

Adult subjects with CRF and anemia, receiving PD, clinically stable, Hgb < 10.0 g/dL, no EPO therapy within 3 months before the planned first dose of ARANESP or EPO.

Study Endpoints:

Primary:

Part A: Hgb ROR over initial 4 weeks of treatment
Part B: Hgb level after 16 weeks of treatment
Safety: Nature, frequency, severity, relation to treatment, and outcome of all AEs

Secondary:

Part A: Change in hematocrit, RBC count, and reticulocyte count over the initial 4 weeks of treatment
Part B: Hematocrit, RBC count, and reticulocyte count after 16 weeks of treatment
Maintenance Period: Hgb, hematocrit, RBC count, and reticulocyte count
Safety: Clinical laboratory findings (hematology, coagulation, iron status, biochemistry), vital signs, and treatment exposure

Results:

Sixty-six (66) subjects were randomized; all received study agent. At interim analysis, all subjects had been enrolled and had completed 4 weeks of treatment in Part A, allowing analysis of the primary study endpoint. In accordance with the recommendations of the Safety Monitoring Committee (SMC), dose-escalation was stopped at 0.75 μg/kg/wk. Doses of 1.5 μg/kg/wk were open only to subjects who failed to demonstrate a response to 0.75 μg/kg/wk. When 30 subjects had been enrolled at 0.75 μg/kg/wk, the SMC recommended that enrollment be discontinued in this dose cohort, and re-opened in the 0.45 μg/kg/wk QW cohort.

In total, there were 81 subject exposures among 66 subjects. For subjects receiving ARANESP, there were 6 subject exposures at 0.075 μg/kg/wk, 10 at 0.225 μg/kg/wk, 22 at 0.45 μg/kg/wk, 30 at 0.75 μg/kg/wk, and 4 at 1.5 μg/kg/wk. Nine (9) subjects received EPO (100 U/kg/wk). The

sponsor terminated the EPO comparison phase of the study early, following the initiation of other EPO active-control investigations.

Efficacy Results:

Part A:

There was a significant dose-related effect of ARANESP on the Hgb ROR, hematocrit, RBC count, and reticulocyte count over the initial 4 weeks of study. During the dose-escalation phase of the study, the mean Hgb ROR over the initial 4 weeks was 0.31 g/dL (95% CI: -0.27, 0.89) for the 0.225 μg/kg/wk cohort, 1.12 g/dL (95% CI: 0.59, 1.65) for the 0.45 μg/kg/wk cohort, and 1.44 g/dL (95% CI: 1.10, 1.77) for the 0.75 μg/kg/wk cohort. No interaction was observed between baseline Hgb and the Hgb response. The Hgb ROR over the initial 4 weeks appeared similar for ARANESP and EPO at the selected doses, although the number of subjects in the comparison was small.

Part B:

For the 48 subjects who responded to ARANESP in Part A and continued treatment, no significant differences were observed in either dose or schedule for Hgb, hematocrit, RBC counts, or reticulocyte counts after 16 weeks of dosing.

Maintenance Period:

The mean Hgb was maintained between 10 and 13 g/dL for the 34 subjects who continued ARANESP dosing into the Maintenance Period. Mean hematocrit, RBC counts, and reticulocyte counts were also stable.

Safety Results:

Fifty-seven (57) subjects received ARANESP, with a median exposure time of 28 weeks. The median exposure time was 10 weeks for the 9 subjects who received EPO.

Adverse Events

Adverse events were reported in 88% of ARANESP-treated subjects, with serious and severe adverse events reported in 40% and 30% of ARANESP-treated subjects, respectively. There were 2 deaths: 1 on-study death was attributed to acute myocardial infarction (MI), and another was attributed to bronchial pneumonia after withdrawal from the study. Adverse events were not atypical of a CRF population receiving PD. The most commonly reported AEs were injection site pain (32%), HTN (30%), peripheral edema and peritonitis (28%, each), fluid overload (26%), dizziness (19%), and diarrhea and vomiting (18%, each).

Severe Adverse Events

Four (4) severe adverse events were reported on >1 occasion: peritonitis (9%), fluid overload (5%), myocardial infarction (5%), and intestinal obstruction and gangrene (4%, each). Other severe adverse events were isolated.

Serious Adverse Events

The most frequent SAEs were peritonitis (14%), fluid overload (9%), and myocardial infarction and dyspnea (both 5%). Diarrhea, intestinal obstruction, pleural effusion, dehydration, lower respiratory tract infection, and gangrene were each reported in 4% of subjects. Other SAEs were reported only once.

Reviewer's Comments: In light of the limited sample sizes and open-label study design, a meaningful comparison of treatment groups is not plausible. Moreover, rates for the more

subjective AEs must be interpreted in light of the open-label study design. These data are included in CBER's integrated analysis of safety.

ARANESP Antibodies
The median time from the first dose of ARANESP to the last antibody sample was 38.5 weeks (range, 5 to 73; n = 56). All assay samples were negative.

Summary for Protocol 960246:

The interim analysis of this open-label, dose-escalation study suggests that ARANESP administered SC QW or TIW supports erythropoiesis in subjects with CRF and anemia receiving PD. There was a dose-related effect of ARANESP on Hgb ROR over the initial 4 weeks of treatment. ARANESP doses of 0.45 μg/kg/wk and 0.75 μg/kg/wk were associated with mean Hgb rates of rise of ≥ 1 g/dL and < 3 g/dL over the initial 4 weeks (≥ 0.25 to 0.75 g/dL/week). There was no apparent difference in response between the QW and TIW administration schedules. The results suggest that weekly SC ARANESP at a dose of 0.45 to 0.75 μg/kg/wk may be an appropriate starting dose for treatment of anemia in this CRF population.

Phase 2 Efficacy Studies for Correction of Anemia:

Overview:

The North American protocol 980211 and the European (and Australian) protocol 980202 are the phase 2 studies designed to assess the efficacy and safety of ARANESP in anemic subjects with CRF - - subjects who are EPO-naïve. *These studies provide the core of evidence in support of the efficacy and safety of ARANESP in anemic subjects with CRF.* The studies share similarities in their objectives, designs and patient populations, and are presented together in this review. Where appropriate, the studies are compared and contrasted. For the purpose of this review, protocols 980211 and 980202 are referred to as Studies "211" and "202," respectively.

Study 211 – North American Phase 2 Study in EPO-Naïve Subjects:

Title:	An Open-Label Randomized Study of ARANESP and Recombinant Human Erythropoietin (r-HuEPO) for Treatment of Anemia in Patients With End-Stage Renal Disease Receiving Dialysis
Study Period:	November 1998 – ongoing; interim data cutoff October 5, 1999
Centers:	Nineteen (19) centers in the U.S.
Subjects:	122 randomized

This phase 2 study was conducted under IND -----.

Notes:
1. Interim analyses, on data collected through 8/31/99, were provided with the 12/28/99 BLA submission. A second study report, with final efficacy analyses of data collected through 10/5/99, was provided in response to CBER's Discipline Review letter of 12/15/00 (Amendments No. 20 [paper] and 21 [---------- 12/28/00).

2. Subsequently, in response to a CBER query on 5/14/01, the sponsor discovered that Amendment No. 21 contained the *interim* rather than the *final* case report tabulations,

which had been inadvertently re-submitted with an updated archive date. The sponsor then submitted the *final* case report tabulations as amendment 033, which were received by CBER on 5/17/01.

3. This review document reflects all data submitted through 5/17/01.
4. Accrual of extended safety data is ongoing.

Study 202 – European Phase 2 Study in Pre-Dialysis, EPO-Naïve Subjects:

Title: A Randomized Study of ARANESP and Recombinant Human Erythropoietin (r-HuEPO) for Treatment of Anemia in Predialysis Chronic Renal Failure Subjects
Study Period: December 1998 – ongoing; interim data cutoff October 5, 1999
Centers: Thirty-six (36) centers in Europe and Australia
Subjects: 166 randomized

Study 202 was not conducted under IND.

Notes:

1. Interim analyses, as of 7/31/99, were provided with the 12/28/99 BLA submission. A second study report, with final efficacy analyses through 10/5/99, was provided with Amendment No. 20 (paper) and 21 (----------), 12/28/00.
2. Accrual of extended safety data is ongoing.

Objectives:

Both studies are designed to assess the effectiveness and safety of ARANESP in treatment of anemia in subjects with ESRD who have not been treated with EPO within 12 weeks ("EPO-naive" subjects). Aside from the geographic difference in subject populations, a primary difference between studies is the use of dialysis. Study 211 was designed to evaluate ARANESP in ESRD subjects who are receiving dialysis, whereas Study 202 enrolled subjects who were not on dialysis, presumably earlier in the course of their disease ("pre-dialysis" subjects).

Study Designs:

These are multicenter, randomized, open-label, parallel-group studies. For both studies, enrollment is complete; however, extended safety follow-up is ongoing.

Study 211: Subjects (n=120) with CRF, on dialysis, were randomized 3:1 to receive 0.45 μg/kg of ARANESP QW or 50 U/kg of EPO administered TIW for 20 weeks. The route of administration was IV or SC, depending on dialysis unit policy. Subjects are to complete a 1-week follow-up period at the end of the study.

Study 202: Subjects (n=160) with CRF, but not receiving dialysis, were randomized in a 3:1 ratio to receive ARANESP 0.45 μg/kg QW, or EPO 50 U/kg BIW for $\leq$ 24 weeks, with both agents to be administered by the SC route. The study was amended to add on optional ARANESP maintenance phase, from weeks 25 – 104, during which ARANESP was to be administered to maintain Hgb between 11 and 13 g/dL. Subjects who initiated dialysis during the study and had completed 52 weeks of ARANESP therapy could be enrolled in the long-term safety dialysis study

(Protocol 980160, see below). For subjects who do not participate in Protocol 980160, end-of-study assessments are to be performed 28 days after the last dose of ARANESP.

For both studies, dose adjustments were to be made, if necessary, to achieve a Hgb increase of ≥ 1.0 g/dL above baseline, to within a target range of 11–13 g/dL. After this target was reached, doses of study agents were to be adjusted to maintain Hgb within the target range, as follows:

- increases by 25% of the starting dose at ≥ 4-week intervals as necessary to achieve target
- adjustments of ± 25% of starting dose, after achieving target, for 2 consecutive out-of-range values
- decreases by 25% of starting dose for Hgb increases of ≥ 2 g/dL over any 4-week period
- increases by 50% of the starting dose for confirmed (by repeat measurement) Hgb < 8 g/dL
- doses withheld for confirmed (by repeat measurement) Hgb >14 g/dL, until Hgb <12 g/dL, at which time study agents to be restarted at a dose 25% lower than the dose at the time the study agent was discontinued.
- adjustments at investigator's discretion when clinically indicated

Randomization was performed via a central interactive voice response system. Each study center used commercial recombinant erythropoietin supplied by its pharmacy.

Study Agents:

The starting ARANESP dose of 0.45 μg/kg QW was selected for Study 211 on the basis of preliminary analyses of protocols 960245 and 960246. The same starting dose was selected for Study 202, based on the assumption that the ARANESP dose requirements should be similar for dialysis and pre-dialysis patients. ARANESP was supplied in ~1.0 mL vials containing 20 or 100 μg ARANESP per mL, and human serum albumin, intended for single-dose use.

EPO was administered at a starting dose of 50 U/kg on a TIW schedule in Study 211, and a BIW schedule in Study 202. (Twice weekly EPO administration was chosen for Study 202 because it was the most common regimen in clinical practice at centers participating in the study.) EPOGEN® (Amgen) was used exclusively in Study 211, whereas ----------) was used in Study 202. ----------) was not used in either study.

Minor differences in study designs include:

- Subjects received test agents by the SC or IV route in Study 211; the SC route was used exclusively in Study 202.
- Starting ARANESP doses were equivalent in the 2 studies; however, the starting EPO dose was 150 U/kg/week in Study 211, but only 100 U/week in Study 202.
- Study 202 included a prolonged, optional maintenance phase (weeks 25 – 104). This was not a feature of Study 211.

Study Entrance Criteria:

Study 211: The study population includes adult subjects with CRF, receiving dialysis, with at least moderate anemia (Hgb ≤ 10 g/dL). Subjects were to be EPO-naïve (no EPO therapy allowed within 12 weeks before the initial planned dose of study agent). Subjects were to have adequate transferrin saturation (≥ 20%), or should have received IV iron therapy 2 weeks before the first

dose of study agent. Serum vitamin B_{12} and RBC folate levels were to be above the lower limit of normal. Exclusion criteria included:

- uncontrolled HTN
- congestive heart failure (New York Heart Association functional class III or IV)
- grand mal seizures within 2 years
- clinical evidence of severe hyperparathyroidism
- major surgery (excluding access surgery) within 12 weeks
- systemic hematologic diseases (e.g., sickle cell anemia, myelodysplastic syndromes, hematologic malignancy, myeloma, hemolytic anemia)
- systemic infection, active inflammatory disease, malignancy, hepatic enzymes >2X the upper limit of normal
- known hypersensitivity to human albumin
- androgen therapy with 8 weeks

Study 202: The patient population was very similar to that of Study 211, except that the investigation was planned to evaluate ARANESP in pre-dialysis subjects (creatinine clearance < 30 mL/min), with less severe anemia (Hgb < 11 g/dL). Subjects were to be EPO-naïve, with initiation of dialysis not expected until ≥ 24 weeks after the initial dose of study agent.

Reviewer's Comment: Presumably, relative to subjects in Study 202, subjects in Study 211 have more advanced renal impairment (hence the need for dialysis), lower endogenous EPO levels, and more severe anemia. Moreover, the HD patients of Study 211 are predisposed to blood loss as a result of dialysis.

Concomitant Medications, Transfusions:

Concomitant medications or treatments were to be provided as deemed necessary. RBC transfusions were not permitted during the 1-week screening period, but were allowed during the study treatment period. Subjects were to be withdrawn if they received androgen therapy and/or investigational drugs other than ARANESP. Subjects with serum ferritin < 100 ng/mL (and/or transferrin saturation < 20% in Study 211, only) were to receive IV iron therapy according to unit policy; oral iron therapy was permitted throughout the study.

Monitoring:

Durations of monitoring were 20 and 24 weeks in Studies 211 and 202, respectively. Hematology studies were obtained weekly in Study 211, and at 2-week intervals in Study 202, with samples analyzed by a central laboratory. In both studies, vitals signs were assessed at 2-week intervals, and iron status was determined at 4-week intervals. Serum chemistries and antibody status were assessed at mid-study and end-of-study. Measurements of study agent concentrations were to be performed at 4-week intervals in Study 202, but were not performed as part of Study 211.

Immunogenicity:

Two assays were developed to detect ARANESP antibodies: a ---------- screening assay to detect immunoreactivity to ARANESP or EPO, and a ---------- detect neutralizing antibodies. In the screening assay, serum samples were assayed for seroreactivity to ARANESP or EPO using a standard ---------- assay using ---------- ----------. Results were to be expressed in ---------- ----------). A sample was to be considered positive if ---------- the pre-dose value in 2 independent screening assays. The screening assay was to be repeated using a second aliquot

of the same sample if the initial sample tested positive, and the titer was to be determined. Confirmation of seroreactivity would then be established by repeating the above procedure on a serum sample drawn from the subject at a later time point. If 2 sequential serum samples were seroreactive, both samples would be submitted for ---------- to ascertain the presence of ---------- antibodies. The latter ---------- was based on ---------- of a ----------. Serum samples were to be considered ---------- of control ---------- independent assays. Results were to be expressed as the serum titer at which ---------- was observed.

Study Endpoints:

Primary:

The primary efficacy endpoint was the proportion of subjects achieving a Hgb target, defined as a Hgb increase of ≥ 1.0 g/dL from baseline and a Hgb concentration ≥ 11.0 g/dL during the study. The time points for assessment of the endpoint were 20 and 24 weeks in Study 211 and 202, respectively.

The studies were designed to provide supportive evidence of efficacy of ARANESP in treating anemia, and were not powered to make formal comparisons between treatment groups. The sponsor selected a minimum acceptable Hgb response rate of 50% as representing a response in a "clinically meaningful" proportion of subjects. Subjects who withdrew from the study before achieving the Hgb target were considered as not having achieved the target.

Reviewer's Comments: The sponsor describes these studies as providing "supportive evidence" of efficacy of ARANESP in treating anemia. They are, however, the only studies supporting the efficacy of ARANESP in CRF patients with anemia. Of note, there are no data to support the arbitrary designation of a 50% response rate as providing evidence of a "clinically meaningful" response.

For descriptive purposes, the primary endpoint was analyzed by subgroups defined by covariates of: age (<65, ≥65, ≥75), gender, race, route of study agent administration (Study 211, only), modality of dialysis (HD, peritoneal dialysis [PD] – Study 211, only), length of time on dialysis (Study 211, only), primary cause of renal failure, baseline Hgb (Study 211, only), iron status (Study 211, only) and baseline creatinine clearance (Study 202, only).

Secondary:

- Hgb at 4-week intervals
- change in Hgb from baseline at 4-week intervals
- time to initial achievement of Hgb target
- dose of study agent when target Hgb is reached and at week 20 (Study 211); week 24 (Study 202)
- number of subjects receiving RBC transfusions and transfusions/subject

Safety:

- percentage of Hgb values outside target range (<11, >13 g/dL) after initially within target range

- number of Hgb increases ≥ 3 g/dL (Study 211) or ≥ 2 g/dL (Study 202) within any 4-week period
- maximum increase in Hgb within any 4-week period
- change in Hgb after 4 weeks of treatment (Study 211)
- AEs, changes in laboratory values and vital signs, incidence of antibody formation

Definitions of Study Populations:

A modified intent-to-treat (mITT) analysis set was defined as all randomized subjects who received ≥1 dose of the study agent to which they were assigned.

Reviewer's Comment: Subjects who were randomized and who received ≥1 dose of the study agent to which they were assigned do not constitute a modified ITT population. More properly, such subjects comprise a modified "as treated" population. However, for conformity with the sponsor's study report, the "mITT" acronym will be used in this review.

A per protocol (pP) analysis set was to include all randomized subjects who completed the study (Study 211) or who completed 16 weeks of treatment (Study 202), who received 75-125% of the total prescribed dose of study agent, ≤ 1 dose of the incorrect study agent, and no RBC transfusions. An additional requirement was the completion of ≥ 75% of protocol-specified post-baseline Hgb measurements.

A safety analysis set was defined as all randomized subjects who received ≥1 dose of study agent; subjects who received ≥1 ARANESP dose were included in the ARANESP group.

The primary efficacy analysis and time to achieve the Hgb target were performed with the mITT analysis set, the completed subjects analysis set, and the pP analysis set (see below). Hemoglobin concentrations during the treatment period, change in Hgb from baseline, dose of study drug, number of subjects receiving RBC transfusions, and the number of RBC transfusions per subject were analyzed using the mITT analysis set only. Additional descriptive analyses of the primary endpoint and time to achieve the Hgb target were performed using the subset of subjects who completed the study and the per-protocol (pP) analysis set.

Interim Analyses:

For both studies, interim analyses were performed to support the filing of this BLA. There was no intention of stopping either trial early as a result of these analyses, and no adjustments for confidence intervals were planned. CBER requested the final data from these studies in its Discipline Review letter of 12/15/00. Final efficacy data were submitted on 12/28/00 and 5/17/01, and are reviewed in this document.

Protocol Amendments:

There were three protocol amendments for Study 211, dated 10/21/98, 12/9/98, and 2/24/99. These were minor and had no material effect on study conduct or planned analyses.

Study 202 was amended on 3/31/99 to extend the treatment duration for subjects randomized to ARANESP. Upon completion of 24 weeks of ARANESP therapy, subjects had the option to continue ARANESP treatment for up to 104 weeks. In addition, subjects who began dialysis while receiving ARANESP and completed 52 weeks of treatment could be enrolled in a long-term safety

study in dialysis subjects (protocol 980160). Subjects randomized to EPO received treatment through week 24, only. The amendment also included a provision to perform a full analysis of safety and efficacy on data obtained through 7/31/99. The statistical analysis plan, dated 6/25/99, directed that the primary and secondary endpoints would be analyzed on data through Week 16, only.

Results:

Enrollment and Disposition of Subjects:

Study 211: The first subject was randomized on 11/30/98, and the last subject completed end-of-study assessments on 10/18/99. One-hundred twenty-two subjects (122) were randomized at 19 study centers: 91 subjects were randomized to ARANESP; 31 subjects were randomized to EPO. Fifteen subjects withdrew from the study: 12 subjects (13%) in the ARANESP group and 3 subjects (10%) in the EPO group. Reasons for withdrawal were similar between treatment groups. Five subjects (5%) in the ARANESP group and 1 subject (3%) in the EPO group died on study. One subject (1%) in the ARANESP group was withdrawn because of an intolerable AE. One ARANESP subject, withdrawn before receiving study agent because of a protocol violation, was excluded from all analyses.

Study 202: The first subject was randomized in December, 1998. A total of 166 subjects were randomized: 129 subjects were randomized to ARANESP, and 37 were randomized to EPO. There were 36 study centers, with geographical distribution as follows: 6 in Germany; 4 each in Australia, Belgium, England and Spain; 3 each in France, Italy and Portugal; 2 in Austria; and 1 in Finland, the Netherlands and Sweden. Discontinuations were as described in Table 2.

Protocol Deviations:

Study 211: Three subjects in the ARANESP group violated inclusion criteria. One subject was identified as an active cocaine user, and was withdrawn before receiving study agent and excluded from all analyses. A subject who had undergone recent cholecystectomy, and another with uncontrolled HTN, were allowed to continue participation in the trial.

Study 202: There were numerous protocol violations in this study:

Table 2: Subject Disposition – Studies 211 and 202

	Study 211		Study 202	
	ARANESP	**EPO**	**ARANESP**	**EPO**
Randomized (n)	91	31	129	37
Received Study Agent [n, (%)]	90 (99%)	31 (100%)	129 (100%)	37 (100%)
Completed Study [n, (%)]	79 (87%)	28 (90%)	42 (33%)	9 (24%)
Discontinued [n, (%)]	11 (12%)	3 (10%)	19 (15%)	6 (16%)
Intolerable AE	1 (1%)	0 (0%)	2 (2%)	0 (0%)
Withdrawal Requested [n, (%)]	2 (2%)	1 (3%)	1 (1%)	2 (5%)
Administrative Decision [n, (%)]	2 (2%)	1 (3%)	10 (8%)	3 (8%)
Death on Study [n, (%)]	5 (5%)	1 (3%)	3 (2%)	1 (3%)
Kidney Transplant [n, (%)]	1 (1%)	0 (0%)	3 (2%)	0 (0%)
Other [n, (%)]	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Did Not Receive Study Agent [n, (%)]	1 (1%)	0 (0%)	0 (0%)	0 (0%)

- One subject was erroneously randomized to EPO because an incorrect center number was provided to the central randomization center.
- Two (2) subjects in the ARANESP group did not have documentation of serum vitamin B_{12} and folate levels at screening. One subject in the EPO group had vitamin B_{12} and folate levels below the lower limit of the normal range during the screening period.
- Three subjects in the ARANESP group incurred major deviations in terms of study agent administered. One subject received 5 times the intended dose of ARANESP in weeks 3 and 4. The subject's Hgb increased from 11.0 g/dL to 14.4 g/dL between weeks 2 and 7, though there were no apparent clinical sequelae. Another subject received 3.5 times the intended dose of ARANESP in week 2. Her Hgb increased from 9.2 g/dL to 12.2 g/dL between weeks 1 and 5. This subject complained of headache and chest pain, which were reported by the investigator as being moderate and possibly related to ARANESP. The third subject was randomized to ARANESP but received 2 injections of EPO in week 17 (this occurred after the subject had achieved a Hgb response).
- A number of subjects in the ARANESP group exhibited evidence of iron deficiency, and/or did not receive appropriate therapy:
    - 2 had screening serum ferritin values < 100 ng/mL but did not receive IV iron before their first dose of study drug. (Of note, both subjects achieved a Hgb response by week 7.)
    - 6 had serum ferritin values < 100 ng/mL while on study, but did not receive IV iron therapy between baseline and week 16, and did not achieve a Hgb response.
    - 3 had screening serum ferritin values < 100 ng/mL and received IV iron in the screening period.
    - 3 had serum ferritin values > 100 ng/mL during the screening period but experienced ferritin values < 100 ng/mL after week 12.

Hemoglobin values could not be verified for the majority of the 12 subjects from one center (center 69). The center was closed, and the sponsor performed a separate analysis of the primary endpoint excluding all subjects from this center.

Study Agent Compliance:

There were major deviations in 3 subjects in this category:

One ARANESP subject received 4 doses of EPO in addition to ARANESP during the study due to staff error. The subject received 8000 U of EPO during weeks 1 and 2 and 18000 U during study week 3. No adverse clinical consequences were reported.

An EPO subject was prescribed EPO BIW for the study period instead of TIW as specified in the protocol. The dosing frequency was further reduced to QW during weeks 5–7, and no study drug was administered during week 11 and weeks 13–16. Despite these errors in the dosing schedule, the subject achieved the Hgb target at week 5 and remained within or above the target range for the remainder of the study.

An EPO subject received the incorrect dose on several occasions during the study due to staff error. The subject received 8300 U instead of 7500 U during week 8, and 5900 U instead of 5100 U during week 11. The subject also received a total of 4 doses (1700 U each) during weeks 12 and 13 after EPO was to have been withheld. There were no apparent adverse clinical consequences.

Baseline Demographics and Disease Status:

Study 211: Baseline characteristics are shown in Table 3. Fifty-four percent of the subjects were male and the majority were of African descent (56%) or Caucasian (34%). Median age was 56.5 years, and 30% of subjects were ≥ 65 years old. The groups were well balanced with respect to baseline characteristics, with the exception of subject weight (median = 81 kg in the ARANESP group; 74 kg in the EPO group). The vast majority of these subjects (93%) were receiving HD, with hypertension and diabetes the most commonly reported causes of CRF. Median time since onset of CRF tended to be shorter in the ARANESP group (3 months) than in the EPO group (11 months), although median time since first dialysis was 1 month in both groups. Mean baseline Hgb was 8.6 g/dL and 8.5 g/dL in the ARANESP and EPO groups, respectively, indicative of significant anemia. In the ARANESP group, 71% of subjects received the study agent by the IV route, and 29% received study agent by SC injection. In the EPO group, subjects were divided equally between IV and SC administration. Baseline blood pressure was balanced between treatment groups (data not shown), with median baseline systolic and diastolic blood pressures of 147 mmHg and 79 mmHg, respectively.

Study 202: The groups were well balanced with respect to demographic characteristics. Fifty-four percent of the subjects were male, and 95% were Caucasian. Median age was 64 years, with approximately half of subjects ≥ 65. The mean baseline Hgb concentration was 0.45 g/dL lower in the ARANESP group (9.33 g/dL) than in the EPO group (9.78 g/dL). Seventy-seven percent of subjects in the ARANESP group and 65% of subjects in the EPO group were iron replete at baseline. There were no notable differences between the treatment groups with respect to baseline creatinine clearance (median = 15 mL/min in both groups) or iron stores. Mean systolic blood pressure at baseline tended to be slightly higher in subjects randomized to ARANESP (155 mmHg) than in those randomized to EPO (141 mmHg).

Reviewer's Comments: The imbalance in baseline Hgb is particularly relevant, in that the higher Hgb in the EPO group increases the likelihood of achieving the Hgb target. Also of note, the median baseline Hgb across the study was ~1 g/dL higher then in the subjects of Study 211, presumably owing to the fact that these subjects had less advanced CRF and were not receiving dialysis.

Paradoxically, serum ferritin levels tended to be lower in Study 202 than in Study 211, suggesting considerable iron repletion in the HD subjects in Study 211.

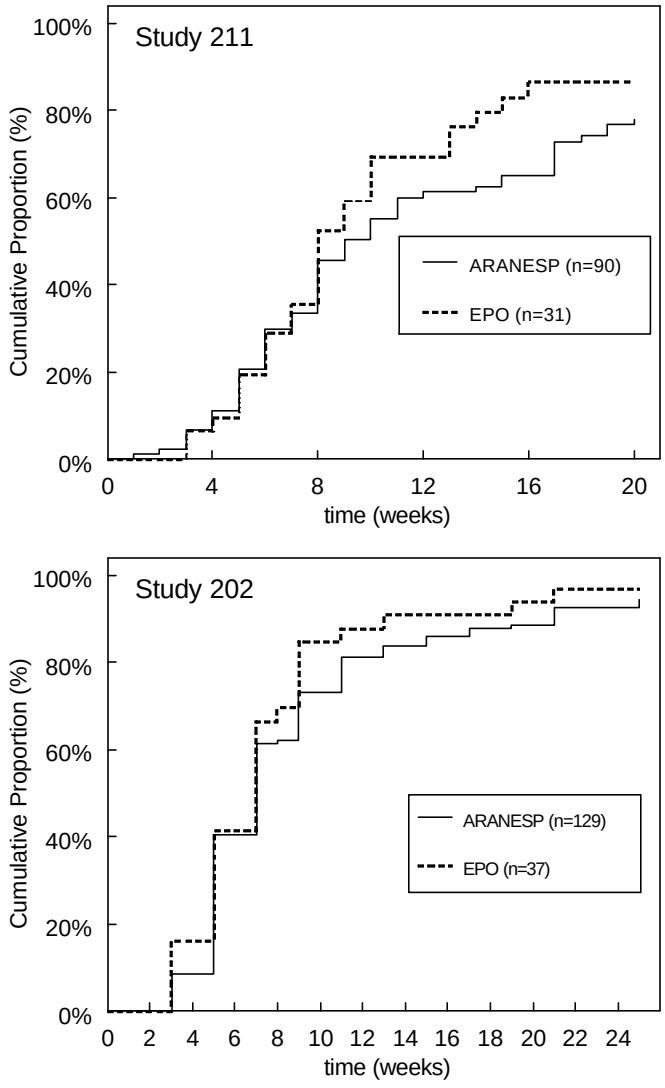
Table 3: Baseline Characteristics – Studies 211 and 202

	Study 211		Study 202	
	ARANESP	**EPO**	**ARANESP**	**EPO**
Number of Subjects	91	31	129	37
Gender [n (%)]				
Female	42 (46%)	16 (52%)	59 (46%)	18 (49%)
Male	49 (54%)	15 (48%)	70 (54%)	19 (51%)
Race [n (%)]				
Asian	2 (2%)	0 (0%)	3 (2%)	1 (3%)
Black	51 (56%)	17 (55%)	3 (2%)	0 (0%)
Caucasian	31 (34%)	11 (35%)	123 (95%)	36 (97%)
Hispanic	6 (7%)	3 (10%)		
Native American	1 (1%)	0 (0%)		
Age [n (%)]				
< 65	65 (71%)	20 (65%)	71 (55%)	19 (51%)
³ 65	26 (29%)	11 (35%)	58 (45%)	18 (49%)
³ 75	8 (9%)	3 (10%)	23 (18%)	8 (22%)
Age (years)				
Mean	55.8	55.4	60.4	60.6
Median (quartiles)	57 (45, 67)	52 (42, 70)	64 (52, 72)	64 (47, 73)
Range	20 - 83	25 - 85	20 - 83	25 - 85
Weight (kg)				
Mean	83.2	72.5	70.4	69.6
Median (quartiles)	80.8 (65.0, 94.0)	74.0 (65.0, 82.6)	70 (62.0, 80.3)	69.0 (60.5, 77.8)
Range	47.0 - 158.0	42.5 - 99.0	37 - 108	45 - 95
Hemoglobin (g/dL)				
Mean	8.59	8.48	9.33	9.78
Median (quartiles)	8.60 (8.05, 9.25)	8.60 (7.75, 9.10)	9.5 (8.7, 10.0)	9.70 (9.3, 10.7)
Range	5.6 - 9.9	6.4 - 9.8	6.6 - 11.0	6.1 - 11.5
Serum Ferritin (ng/mL)				
Mean	353	557	225	210
Median (quartiles)	280 (165 - 443)	431 (223, 726)	168 (106 - 262)	151 (81, 231)
Range	36 - 2044	53 - 1931	30 - 1420	31 - 899
Primary Cause of Renal Failure [n (%)]				
Diabetes	29 (32%)	11 (35%)	32 (25%)	8 (22%)
Hypertension	37 (41%)	11 (35%)	15 (12%)	1 (3%)
Glomerulonephritis	6 (7%)	3 (10%)	24 (19%)	10 (27%)
Polycystic Disease	1 (1%)	1 (3%)	6 (5%)	2 (5%)
Urologic	0 (0%)	1 (3%)	5 (4%)	0 (0%)
Other	10 (11%)	3 (10%)	32 (25%)	11 (30%)
Unknown	8 (9%)	1 (3%)	15 (12%)	5 (14%)
Mode of Dialysis [n (%)]				
Hemodialysis	88 (97%)	26 (84%)	N/A	N/A
Peritoneal	3 (3%)	5 (16%)	N/A	N/A
Route of Study Drug Administration [n (%)]				
IV	64 (71%)	15 (48%)		
SC	26 (29%)	16 (52%)	129 (100%)	37 (100%)
Time Since Onset of Renal Failure (Months)				
Mean	18.9	46.1		
Median (quartiles)	3 (1, 22)	11 (1, 47)		
Range	0 - 236	1 - 344		
Time Since First Dialysis (Months)				
Mean	4.5	12.7		
Median (quartiles)	1 (1, 1)	1 (1, 2)		
Range	0 - 236	0 - 170		

Efficacy Results:

Study 211: The cumulative proportions of subjects achieving the target Hgb are shown in Figure 1 (top panel). For the ARANESP group, the proportion of subjects achieving the Hgb target was 0.72 (95% CI: 0.62, 0.81), whereas for the EPO group the proportion was 0.84 (95% CI: 0.66, 0.95). The difference between groups was not statistically significant; the log-rank p-value is 0.23. The difference between proportions was -0.12 (95% CI: -0.33, 0.09). Given that the lower limit of the 95% confidence interval of the proportion of ARANESP subjects achieving the Hgb target was >0.5 (i.e., 0.62), the primary efficacy endpoint was achieved.

Figure 1: Cumulative Proportion of Subjects Achieving Hgb Target – Study 211 (Top); Study 202 (Bottom)



Exploratory analyses on the effects of prespecified covariates (age, gender, race, route of study agent administration, modality of dialysis, time on dialysis, cause of renal failure, and baseline Hgb) showed a trend indicating an increasing proportion of subjects achieving the Hgb target with increasing baseline Hgb (p=0.06). There was also a trend towards a higher percentage of subjects achieving the Hgb target with SC administration (86%) than with IV administration (70%) (p=0.09). Analyses of the odds ratios for achieving the Hgb target indicated that the effects of baseline Hgb and route of administration were similar for both treatment groups.

The mean calculated increase in Hgb from baseline over the initial 4 weeks of treatment was 1.10 g/dL (95% CI: 0.82, 1.37) for subjects receiving ARANESP and 1.33 g/dL (95% CI: 0.91, 1.74) for subjects receiving EPO.

The median times to achieve the Hgb target (Kaplan-Meier) were 10 and 8 weeks in the ARANESP and EPO groups, respectively.

Reviewer's Comments: The interim analyses, based on 70 subjects in the ARANESP group and 22 subjects in the EPO group, showed a statistically significant difference in favor of the EPO

group in achieving the Hgb target. This suggested that correction of anemia was less rapid or potentially less frequent in ARANESP-treated subjects.

Though this finding is not apparent in the final efficacy analyses, it raised concern, and was the subject of a comment in the Discipline Review letter issued to Amgen 12/15/00. In the original BLA, the sponsor attempted to explain the disparity by noting that the starting dose in the ARANESP group was 40% lower than that of the EPO group on a protein mass basis. Though this may have been the case, it is noteworthy that the starting dose in this study (0.45 μg/kg QW) was identical to the starting dose suggested for correction of anemia in the proposed Package Insert. The sponsor was asked to comment on this point.

The sponsor argued (Amendment A20-8) that the efficacy of ARANESP in EPO-naïve subjects is supported by the final data from Study 211, and supported substantially by the data from Study 202. The Hgb-time relations for ARANESP and EPO in pre-dialysis subjects in Study 202 were similar (see below). In Study 211, Hgb increased with respect to time in both treatment groups, although the increase tended to be slightly greater in subjects receiving EPO after the initial 4 weeks.

Reviewer's Comment: CBER agrees with the sponsor's arguments. Importantly, the studies were neither designed nor powered to demonstrate non-inferiority in a formal statistical sense. The erythropoietic responses to ARANESP and EPO are qualitatively similar in these studies.

Study 202: Similar proportions of subjects achieved a Hgb response in the ARANESP (0.93; 95% CI: 0.87, 0.97) and EPO (0.92; 95% CI: 0.78, 0.98) treatment groups (Figure 1, bottom panel). The lower limit of the CI in the ARANESP group exceeded the minimum targeted response rate of 50%. The mean increase in Hgb from baseline after 4 weeks of treatment was 1.38 g/dL in subjects receiving ARANESP and 1.40 g/dL in subjects receiving EPO, and the median time to Hgb response was 7 weeks (range: 3 to 25 weeks) in both treatment groups.

An analysis of the primary endpoint performed after excluding subjects from the center wherein some Hgb values were missing did not affect the study outcome. Similarly, Hgb response rates did not differ in an analysis that excluded subjects who started dialysis before achieving a Hgb response.

For the mITT analysis set, the unadjusted odds ratio between the treatment groups for achieving a Hgb response was 1.18 (95% CI: 0.30, 4.59). The results of exploratory analyses investigating the effects of pre-specified covariates of age, gender, race, cause of renal failure, baseline Hgb, ferritin, and creatinine clearance on the odds ratio of achieving the Hgb target showed only a significant effect of baseline Hgb on the probability of achieving the target, without a substantial difference between treatment groups.

Reviewer's Comments: These data suggest similar performance for ARANESP and EPO in this patient population. Similar proportions of subjects achieved the Hgb target, despite an imbalance in baseline Hgb concentration that favored the EPO group.

Dose of Study Agent When Hgb Target Achieved and at Week 20/24 (Studies 211/202):

Study 211: The median weekly weight-standardized dose of ARANESP was 0.54 μg/kg at the time the target Hgb was initially achieved (increased ~20% from a starting dose of 0.45 μg/kg). The median weekly weight-adjusted dose was similar for subjects receiving SC and IV ARANESP (0.53 and 0.55 μg/kg, respectively). The median weight-adjusted dose of ARANESP was essentially unchanged at week 20 (0.56 μg/kg; range 0–1.1 μg/kg); however, at week 20 the median weight-adjusted doses for IV vs. SC administration appeared to diverge: 0.65 μg/kg and 0.46 μg/kg, respectively.

The median weekly weight-adjusted dose for subjects receiving EPO (150 U/kg) was essentially unchanged during the course of the study; however, in contradistinction to ARANESP, the median weight-adjusted dose was *lower* with IV EPO administration than with SC EPO administration (150 versus 178 U/kg for the IV and SC routes, respectively).

Study 202: The median weekly dose of ARANESP was 0.46 μg/kg (quartiles 0.45, 0.57 μg/kg) at the time of Hgb response. At Week 24, the median weekly ARANESP dose had decreased to 0.25 μg/kg (quartiles 0.11, 0.46 μg/kg). The median weekly dose of EPO (100 U/kg) did not change during the study.

RBC Transfusions:

Study 211: Twenty-four (24) subjects (27%) in the ARANESP group and 5 subjects (16%) in the EPO group were reported to have received at least 1 RBC transfusion during the study.

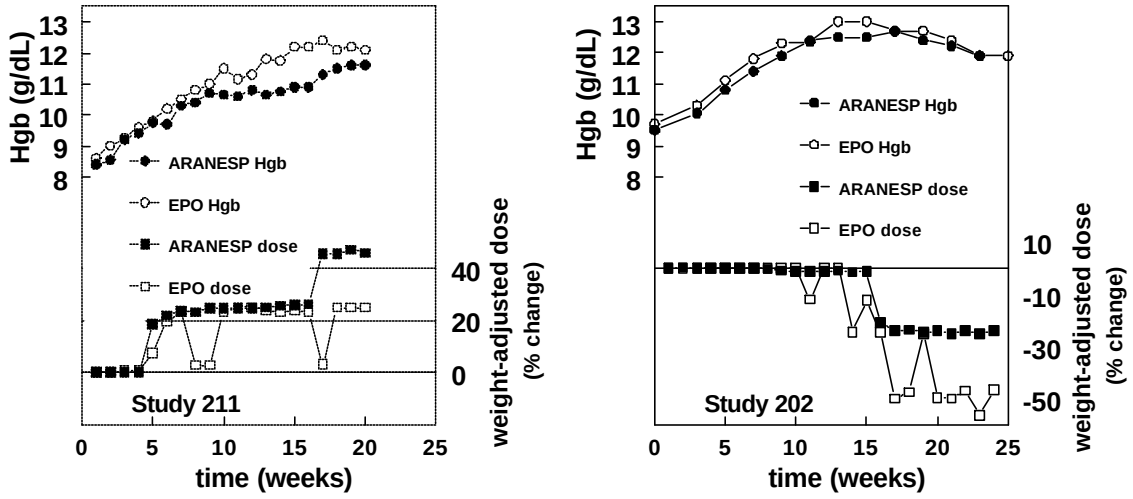
Study 202: Subjects requiring at least 1 RBC transfusion were 5% and 8% in the ARANESP and EPO groups, representing 7 and 3 subjects, respectively.

Reviewer's Comments: The 27% transfusion rate in the ARANESP group in Study 211 is quite substantial. Transfusions were allowed during the study period if "clinically indicated," and after discussion with the study sponsor. This was an open-label trial, and a bias against transfusions may have been operative with respect to the ARANESP group (i.e., a bias towards demonstration of a treatment effect *without the aid of transfusions*). Alternatively, particular investigators, biased towards demonstration of a treatment effect in ARANESP-treated subjects (at any cost) may have been predisposed *in favor of* transfusions. Thus, the 27% transfusion rate is difficult to interpret, and may have been higher or lower had the study been blinded. **In any case, the data do not make the case that ARANESP decreased the need for RBC transfusions, given the directionally opposite trend.** CBER performed a sensitivity analysis to assess the effect of transfusions on the efficacy outcome (see below).

CBER's Exploratory Efficacy Analyses:

Interactions Between Weekly Hgb and Weekly ARANESP Dose:
Figure 2 shows the interaction between median weekly Hgb values and median weekly weight-adjusted doses of study agents for dialysis subjects (Study 211, left) and pre-dialysis subjects (Study 202, right). From a starting ARANESP dose of 0.45 μg/kg, dialysis patients in Study 211 tended to require *increases* in ARANESP dose to reach the target Hgb (Figure 2, left), whereas pre-dialysis patients (Study 202) tended to require dose *decreases* to prevent "overshoot" (Figure 2, right). Though these data were not obtained in concurrently randomized study groups, they do suggest lower ARANESP requirements in pre-dialysis patients, consistent with higher levels of

Figure 2: Relation Between Median ARANESP Dose and Hgb Responses in Dialysis Patients (Study 211, Left) and Pre-Dialysis Patients (Study 202, Right)



endogenous erythropoietin with less advanced kidney disease. Advice to the effect that ARANESP requirements may be lower in pre-dialysis patients would be appropriate for labeling.

Transfusions in Study 211:
As noted above, the 27% transfusion rate in the ARANESP group of Study 211 is substantial, and was higher than the rate in the EPO group (16%). The differential rate could be interpreted as diminished efficacy of ARANESP relative to EPO, delayed onset ARANESP's effect, an inadequate starting dose of ARANESP, or a chance finding.

With respect to transfusions, therefore, CBER performed a "worst case" sensitivity analysis, wherein subjects who received RBC transfusions were considered *not* to have achieved the target Hgb. Of the 29 subjects who received transfusions (24 and 5 subjects in the ARANESP and EPO groups, respectively), 16 were considered to have reached the target Hgb. Thirteen (13) of these subjects were in the ARANESP group; 3 were in the EPO group. When these 16 subjects were considered *not* to have achieved the target Hgb, the proportions of subjects who achieved the target were 0.68 and 0.82 in the ARANESP and EPO groups, respectively. (Kaplan Meier, log-rank = 0.15.) Thus, although RBC transfusions confounded the efficacy results to some extent, the sponsor's "clinically meaningful" response rate of 50% would have been exceeded in the ARANESP group, irrespective of the effect of transfusions.

Safety Results:

Exposure to Study Agents:

Study 211: Ninety (90) and 31 subjects received ARANESP and EPO, respectively. The respective mean times on study agent were 18 and 19 weeks. Approximately 80% of subjects received study agents for ≥17 weeks in both groups.

Study 202: One hundred twenty-nine (129) subjects received ARANESP and 37 subjects received EPO, with a median time of 24 weeks on study agent in both groups. Approximately 80% of ARANESP subjects and 70% of EPO subjects received study agents for >20 weeks.

Deaths:

Study 211: Six deaths occurred on study, with 1 death occurring during the 1-week follow-up period. Five deaths (6%) were reported in the ARANESP group, with 1 death (3%) in the EPO group. All of these subjects had coexisting cardiovascular disease. Causes of death in the ARANESP group included cardiac arrest in 2 subjects, and sudden death, sepsis and "failure-to-thrive'" in 1 subject, each. The sudden death in the ARANESP group was reported to be related to ARANESP by the investigator. This subject was a 72 year-old female who had been hospitalized for uremia. Two days before institution of ARANESP, she had developed atrial tachycardia, which had been attributed to electrolyte imbalance. Apparently, the tachycardia responded to carotid massage, IV adenosine and β-adrenergic blockade. Three days after the initial dose of ARANESP, the subject was found unresponsive and asystolic. Resuscitation attempts were unsuccessful. Autopsy results were inconclusive. The cause of death in the subject assigned to EPO was cardiac arrest.

Study 202: There were 4 deaths on study: 3 in the ARANESP group (2%) and 1 in the EPO group (3%). Deaths on study were primarily cardiovascular in nature; none were considered by investigators to be study agent-related. Two additional subjects who received ARANESP died within 28 days after withdrawal from the study. One subject developed an arrhythmia leading to cardiac arrest 7 weeks after initial exposure to ARANESP. After successful resuscitation, the subject developed hypoxemic brain damage and multi-organ failure. The investigator reported the death as possibly related to ARANESP.

Serious Adverse Events:

Study 211: One or more SAEs were reported in 41% of subjects in the ARANESP group and 35% of subjects in the EPO group. The reported frequencies of individual SAEs were similar between the groups. The range of SAEs was consistent with the CRF patient population, and will be summarized in CBER's integrated summary of safety.

Study 202: Serious adverse events were reported in 42 subjects (33%) receiving ARANESP and 8 subjects (22%) receiving EPO. The most frequent SAE in the ARANESP group was hypertension, reported in 5 subjects (4%), followed by uremia (3%) and cardiac arrest, cardiac failure, dyspnea, chest pain and abnormal renal function (3 subjects, each, for an incidence of 2%). All SAEs reported in the EPO group were single occurrences. Six subjects (5%) in the ARANESP group and none in the EPO group experienced AEs reported by investigators as serious and at least possibly related to ARANESP. Hypertension was the most common SAE to be reported as treatment-related, occurring in 3 subjects (2%). All other SAEs were isolated occurrences.

Of note, a 40-year-old female with a history of diabetes and hypertension, became pregnant 15 weeks after initial exposure to ARANESP. A pregnancy of 4 to 5 weeks gestation was confirmed by ultrasound during a hospitalization at study week 20 for hyperglycemia, hypertension and uremia (Hgb 10.6 g/dL). Concurrently, she experienced gastrointestinal bleeding and refused blood transfusions. One week later, fetal death was confirmed, at a time when the subject's Hgb

was 4.8 g/dL. The investigator reported the fetal death as probably due to severe anemia and diabetes mellitus and not related to ARANESP.

Other Adverse Events:

There were relatively small numbers of subjects in the EPO groups of both studies. Therefore, comparisons between treatment groups with respect to event rates is of limited informativeness, and the reader is referred to CBER's integrated summary of safety for an analysis of AEs by subgroup.

Study 211: One or more AEs were reported in 98% of ARANESP-treated subjects, and 100% of EPO-treated subjects (Table 4). The most frequently reported AEs in the ARANESP group (> 15%) in order of decreasing frequency were nausea, hypertension, myalgia, hypotension, thrombosis of vascular access (TVA), dyspnea, peripheral edema, headache, abdominal pain, vomiting, diarrhea, anemia, and chest pain.
Study 202: One or more AEs were reported in 107 of 129 subjects (83%) in the ARANESP group and 24 of 37 subjects (65%) in the EPO group (Table 4). Treatment related AEs were reported in 29% and 27% of subjects in the ARANESP and EPO groups, respectively. The most frequently reported AEs in the ARANESP group (> 5%) were hypertension, peripheral edema, fatigue, headache, diarrhea and nausea, abdominal pain, arthralgia, myalgia, dyspnea, dizziness, anorexia, chest pain, upper respiratory infection, and pruritus.

Treatment-Related Adverse Events:

Study 211: Adverse events considered by investigators to be possibly, probably, or definitely related to study agent were reported in 22 subjects (24%) receiving ARANESP and 4 subjects (13%) receiving EPO, with most classified as mild to moderate in severity. The most frequent treatment-related AEs were hypertension, reported in 10 subjects (11%) receiving ARANESP and 2 subjects (6%) receiving EPO, and TVA, reported in 6 subjects (7%) receiving ARANESP and no subject receiving EPO.
Study 202: Adverse events considered by investigators to be possibly, probably, or definitely related to study agent were reported in 39 subjects (30%) in the ARANESP group and 10 subjects (27%) in the EPO group. The most frequently reported treatment-related AEs were hypertension (21% ARANESP, 19% EPO) and headache (5% ARANESP, 8% EPO). The greatest difference between treatment groups was observed for the incidence of injection site pain, reported in 8 subjects (6%) receiving ARANESP and no subjects receiving EPO, a disparity that may be related to the open-label study design. Overall, there were no notable differences between groups in the frequencies of treatment-related AEs.

Table 4: Adverse Events With Combined Incidence [3] 5% in ARANESP Groups – Studies 211 and 202

	Study 211		Study 202	
	ARANESP	EPO	ARANESP	EPO
Number of Subjects	90	31	129	37
Number of Subjects Reporting AEs	88 (98%)	31 (100%)	107 (83%)	24 (65%)
Hypertension	28 (31%)	14 (45%)	41 (32%)	8 (22%)
Nausea	29 (32%)	7 (23%)	11 (9%)	5 (14%)
Myalgia	28 (31%)	15 (48%)	9 (7%)	1 (3%)
Edema Peripheral	19 (21%)	8 (26%)	17 (13%)	4 (11%)
Headache	19 (21%)	5 (16%)	14 (11%)	4 (11%)
Diarrhea	16 (18%)	6 (19%)	14 (11%)	3 (8%)
Pain Abdominal	18 (20%)	6 (19%)	11 (9%)	0 (0%)
Dyspnea	19 (21%)	2 (6%)	9 (7%)	3 (8%)
Hypotension	22 (24%)	13 (42%)	3 (2%)	2 (5%)
Dizziness	15 (17%)	6 (19%)	9 (7%)	2 (5%)
Vomiting	18 (20%)	4 (13%)	6 (5%)	1 (3%)
Fatigue	6 (7%)	4 (13%)	16 (12%)	0 (0%)
Pain Chest	14 (16%)	1 (3%)	7 (5%)	1 (3%)
Thrombosis Vascular Access	20 (22%)	4 (13%)		
Anemia	16 (18%)	3 (10%)	2 (2%)	1 (3%)
Edema	11 (12%)	8 (26%)	6 (5%)	1 (3%)
Pain Limb	11 (12%)	3 (10%)	6 (5%)	1 (3%)
Access Complication	11 (12%)	4 (13%)	5 (4%)	0 (0%)
Access Infection	10 (11%)	0 (0%)	6 (5%)	1 (3%)
Anorexia	7 (8%)	2 (6%)	9 (7%)	1 (3%)
Pruritus	9 (10%)	3 (10%)	7 (5%)	4 (11%)
Arthralgia	5 (6%)	4 (13%)	10 (8%)	3 (8%)
Asthenia	11 (12%)	4 (13%)	4 (3%)	1 (3%)
Infection Upper Respiratory	8 (9%)	6 (19%)	7 (5%)	1 (3%)
Cough	7 (8%)	1 (3%)	6 (5%)	2 (5%)
Fever	9 (10%)	2 (6%)	4 (3%)	0 (0%)
Malaise	10 (11%)	5 (16%)	3 (2%)	0 (0%)
Pain Back	10 (11%)	6 (19%)	3 (2%)	2 (5%)

Hypertension, Acute MI, TIA, TVA, Seizures, Cerebrovascular Disorders:

The reported incidences of hypertension, acute MI, transient ischemia attack (TIA), TVA, convulsions, and cerebrovascular disorder are summarized in Table 5. Though there are differences in reported incidences for some of these events, the numbers of subjects in the EPO groups are so small as to limit the meaningfulness of these comparisons. For an overall analysis of these events, see CBER's integrated analysis of safety.

Severe Adverse Events:

Study 211: Adverse events considered to be severe, life-threatening, or fatal were reported in 38 subjects (42%) in the ARANESP group and 9 subjects (29%) in the EPO group. Events in the ARANESP group with a reported frequency of > 1 include: hypertension (10 events, 11%), anemia (5 events, 6%), TVA (3 events, 3%), and bradycardia, cardiac arrest, MI, access hemorrhage, access stenosis, and myalgia (2 events, each; 2%). Other than myalgia (3 events, 10%), all severe adverse events in the EPO group were isolated.

Table 5: Reported Incidences of HTN, Acute MI, TIA, TVA, Seizures and Cerebrovascular Disorders – Studies 211 and 202

	Study 211		Study 202	
	ARANESP	EPO	ARANESP	EPO
Numbers of Subjects	90	31	129	37
Hypertension	28 (31%)	14 (45%)	41 (32%)	8 (22%)
Myocardial Infarction	4 (4%)	0 (0%)	1 (1%)	0 (0%)
Transient Ischemic Attack	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Thrombosis Vascular Access	20 (22%)	4 (13%)	0 (0%)	1 (3%)
Convulsions	3 (3%)	1 (3%)	0 (0%)	0 (0%)
Cerebrovascular Disorder	2 (2%)	0 (0%)	0 (0%)	0 (0%)

Study 202: Adverse events considered to be severe, life-threatening, or fatal were reported in 28 subjects (22%) in the ARANESP group and 6 subjects (16%) in the EPO group. The following events had the highest incidence in subjects receiving ARANESP: cardiac arrest, cardiac failure and hypertension (3 subjects each, 2.3%); and chest pain, fever, and arthralgia (2 subjects each, 1.6%). Renal failure/uremia was also reported in several subjects. The 6 events considered to be severe, life-threatening, or fatal in the EPO group were all isolated.

Though there were slight disparities in the rates of severe adverse events between the treatment groups, the small sample sizes in the EPO groups limit the informativeness of these comparisons. See CBER's integrated analyses of safety for additional information.

Withdrawals Due to Adverse Events:

Study 211: There was a single withdrawal due to profuse hemorrhage from a broken central venous access port in the ARANESP group. The event was deemed unrelated to study agent.

Study 202: There were 2 withdrawals due to AEs in the ARANESP treatment group, and both subjects died after withdrawal from the study. One subject developed an arrhythmia leading to cardiac arrest and multi-organ failure that was reported as possibly related to ARANESP. Another subject was withdrawn after diagnosis of metastatic cancer from an unknown primary site.

Percentage of Hemoglobin Values Outside of Target Range:

Study 211: The median percentage of Hgb concentrations outside the target range was 40% in the ARANESP group and 50% in the EPO group.

Reviewer's Comments: Subjects who exceed a Hgb concentration of 13 g/dL (the upper limit of the target Hgb for this study) may incur increased risk of AEs. For the 90 subjects randomized to ARANESP, CBER found that 27% of subjects experienced Hgb values >13 g/dL at some point during the study, and 16% experienced Hgb values in excess of 14 g/dL. Thus, for the ARANESP group, 46% of subjects achieved the target Hgb without "overshoot," 27% reached the target but ultimately experienced Hgb values >13 g/dL, and 28% of subjects failed to achieve the target Hgb. For the EPO group, 29% of subjects achieved and did not exceed the target Hgb, 55% exceeded the target, and 16% failed to reach the target.

Study 202: For the both treatment groups, approximately 40% of recorded Hgb values were outside the target range.

Reviewer's Comments: For the ARANESP group, CBER found that 25% of subjects reached and did not exceed the Hgb target of 13 g/dL, 62% reached but exceeded the target, and 13% failed to reach the target. For the EPO group, 8% of subjects reached and did not exceed the target, 78% reached but exceeded the target, and 14% failed to reach the target. Hgb values in excess of 14 g/dL were experienced by 25% and 35% of subjects in the ARANESP and EPO groups, respectively. **The fact that 62% and 78% of subjects in the ARANESP and EPO treatment groups, respectively, exceeded the upper limit of the Hgb target range suggests that these starting doses were excessive for a pre-dialysis patient population.**

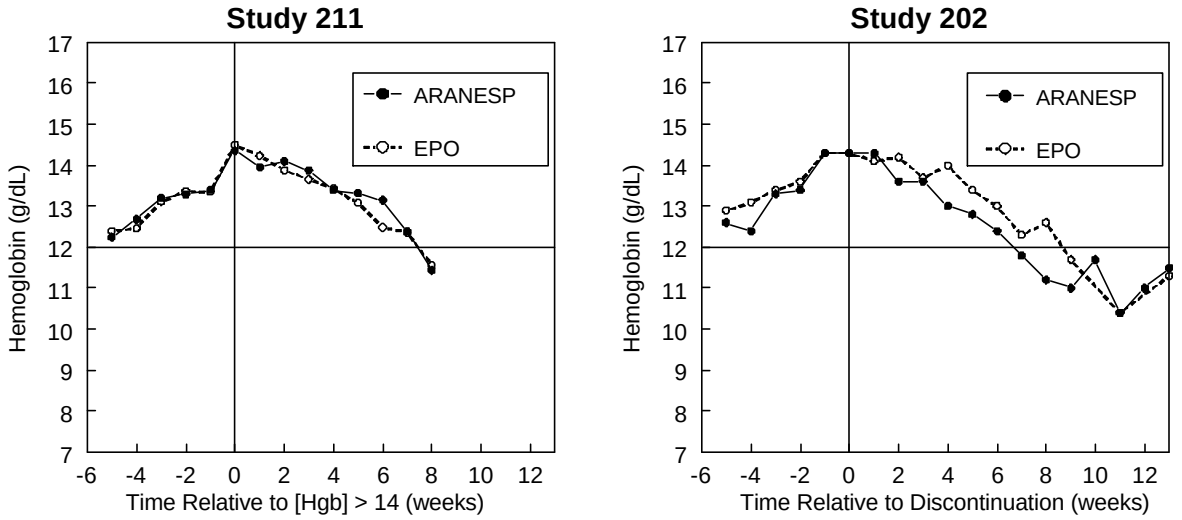
Effect of Withholding Doses for Hemoglobin in Excess of 14 g/dL:

Study 211: For subjects with reported Hgb values in excess of 14 g/dL, the sponsor reported median times required for Hgb values to decrease to ≤ 12.0 g/dL of 8 weeks (range: 5–9 weeks) in the ARANESP group and 8 weeks (range: 2–9 weeks) in the EPO group.

Study 202: Discontinuation of study agent for Hgb > 14.0 g/dL was reported in 44 subjects (31 ARANESP [24%], 13 EPO [35%]). For these subjects, the median time required for Hgb to decrease to ≤ 12.0 g/dL was 7 weeks (range: 2–13 weeks) in the ARANESP group and 9 weeks (range: 6–13 weeks) in the EPO group.

Reviewer's Comments: The sponsor's analyses in Study 211 included only non-censored subjects. For Study 211, CBER assessed the Hgb-time relation in all subjects who reached a Hgb concentration of > 14 d/dL, (Figure 3, left), and the Hgb-time relations in the 2 treatment groups were virtually superimposable. The slopes (least squares analysis) after exceeding a Hgb concentration of 14 d/dL were essentially the same: -0.31 g/dL per week in the ARANESP group, and –0.34 g/dL per week in the EPO group. For both agents, therefore, the rate of Hgb decrease after discontinuation was ~1 g/dL over 3 weeks. The similarity of the Hgb-time relations in the two treatment groups after withdrawal of study agent suggests that this relation is largely determined by the kinetics of RBC survival, and not the biological half-life of ARANESP or EPO. Given that RBC survival is measured in months, whereas the half-lives of the study agents are measured in hours, this finding is not unexpected. The slopes of the Hgb versus time relations in Study 202 were quite similar (Figure 3, right).

Figure 3: Effect of Study Agent Discontinuation on Mean Serum Hemoglobin:



ARANESP and EPO Antibodies:

Study 211: Serum samples for the detection of antibodies to ARANESP or EPO were collected at baseline, week 10, at end of study. Post-baseline serum samples for antibody testing were available for 85 subjects (94%) in the ARANESP group at a median exposure time of 21 weeks (range: 4–21 weeks), and for 31 subjects (100%) in the EPO group at a median exposure time of 21 weeks (range: 7–21 weeks). Five subjects (6%) discontinued from the study before a post-dose antibody sample was drawn. No antibodies were detected for any sample.

Study 202: Serum samples for the detection of antibodies to ARANESP or EPO were collected at baseline, and at 12-week intervals throughout the study. Post-baseline serum samples for antibody testing were available for all 129 subjects in the ARANESP group at a median exposure time of 25 weeks (range: 5–29 weeks) and for 35 of 37 subjects (95%) in the EPO group at a median exposure time of 28 weeks (range: 5–29 weeks). Two subjects discontinued from the study before a post-dose antibody sample was obtained. Antibody assays were negative for all samples tested.

Vital Signs:

The sponsor evaluated upward and downward shifts in systolic and diastolic blood pressure from baseline in increments of 10 mmHg, and performed similar analyses for heart rate. Although there was considerable within-subject variation, there were no trends suggesting meaningful alterations in blood pressure or heart rate in response to these agents in either study.

Iron Parameters:

Study 211: Seventeen percent (17%) of subjects in the ARANESP group and 6% of subjects in the EPO group were iron deficient at baseline (defined as serum ferritin <100 ng/mL or transferrin saturation <20%). The incidence of subjects with iron deficiency at any time during the study was

78% in ARANESP-treated subjects and 81% in EPO-treated subjects. Ninety-two percent (92%) of subjects in the ARANESP group and 81% of subjects in the EPO group received IV iron. At End-of-Study, 38% and 24% of subjects were iron deficient in the ARANESP and EPO groups, respectively.

Study 202: Twenty-three percent (23%) of subjects in the ARANESP group and 35% of subjects in the EPO group were iron deficient at baseline (as defined by serum ferritin < 100 ng/mL). The incidence of subjects with iron deficiency at any time during the study was 78% in subjects receiving ARANESP and 76% in subjects receiving EPO. Seventy-seven percent (77%) of subjects in the ARANESP group and 81% of subjects in the EPO group received IV iron. At End-of-Study, 18% and 39% of subjects were iron deficient in the ARANESP and EPO groups, respectively.

Reviewer's Comment: The rates of iron deficiency are substantial in both treatment groups and in both studies, and underscore the need for careful monitoring and iron repletion in these patients.

Anti-Hypertensive Medications:

Study 211: Ninety-three percent (93%) of subjects in the ARANESP group and 94% of subjects in the EPO group received antihypertensive medications during the study, and the majority had some modification to their regimen. In terms of the numbers of anti-hypertensive medications and their dosages, there tended to be excess additions relative to subtractions for the ARANESP group. For the EPO group, dose decreases were slightly more frequent than dose increases; however, this trend was counterbalanced by a trend towards excess medication additions (vs. subtractions). In light of these divergent trends and the limited sample size of the EPO group, differences between treatment groups can not be adequately evaluated.

Study 202: Antihypertensive medication use was reported for a similarly large proportion of subjects in both treatment groups (91% ARANESP, 84% EPO). In both treatment groups, there appeared to be intensification of anti-hypertensive therapy, with slight excesses of additions relative to subtractions, in terms of both the dosages and numbers of anti-hypertensive medications. There was no apparent difference between groups in this regard, although the limited sample size of the EPO group limits the strength of this comparison.

Clinical Pathology:

Study 211: Though a minority of subjects experienced outlying laboratory values, analysis of shift tables did not suggest any apparent trends related to study agents.

Study 202: Changes in biochemical variables from baseline to the end of the study were similar between treatment groups throughout the study. There were no notable shifts in values for any variable.

Discussion and Analysis – Studies 211 and 202:

Studies 211 and 202 are the active-control studies that constitute the core of evidence of efficacy and safety for ARANESP for the treatment of anemia associated with CRF. The studies were designed to provide supportive evidence of the performance of ARANESP in the CRF population, and were not intended to provide formal, statistically rigorous, non-inferiority comparisons between ARANESP and EPO. Study 211 was powered to show achievement of a Hgb target in a "clinically meaningful" (≥ 50%) proportion of ARANESP-treated subjects, though data to support

the selection of a 50% response rate as being "clinically meaningful" were not provided. Study 202 did not provide a pre-specified minimum rate of response.

Study 211 assessed the performance of ARANESP in a CRF population receiving dialysis, whereas subjects in Study 202 were not receiving dialysis. Generally, therefore, relative to the patient population of Study 202, the patient population of Study 211 would be expected to have: 1) farther advanced renal parenchymal disease; 2) lower levels of endogenous erythropoietin; 3) more severe anemia at baseline; 4) greater demands from blood loss (related to hemodialysis); and 5) lower iron stores. Of the two studies, therefore, Study 211 provided the more rigorous test of the efficacy of ARANESP. The study is also particularly relevant because the starting dose used (0.45 μg/kg/week) was equivalent to the starting dose proposed for correction of anemia in the Package Insert.

Although ARANESP appears to have efficacy for the correction of anemia in the CRF dialysis population of Study 211, the magnitude of the observed effect is not overwhelming. Though 72% of subjects in the ARANESP group achieved the Hgb target (compared to 84% of EPO-treated subjects), the strength of the data has to be considered in light of the following factors:

- 20 weeks were allowed for subjects to reach the Hgb target
- 4 opportunities were available for dose increases during the course of the study
- 27% of ARANESP subjects received ≥1 RBC transfusion
- ≥ 1/3 of the subjects who achieved the lower limit of the Hgb target range (11 g/dL) overshot the target range, experiencing Hgb concentrations in excess of 13 g/dL.

Subjects in Study 211 tended to require increases in ARANESP dose to reach the target Hgb range, from a median dose of 0.45 μg/kg/week at initiation of therapy to 0.56 μg/kg/week at End-of-Study. Though use of a higher starting dose could have increased the proportion of patients who reached the target Hgb concentration, the selection of a higher starting dose would have likely resulted in more frequent "overshoots," with increased risk of AEs. Thus, the use of a 0.45 μg/kg/week starting dose appears to constitute a reasonable compromise. The data do not appear to suggest different dosing requirements for SC versus IV ARANESP administration, although this is not a firm conclusion given that only 26 dialysis subjects received the product by the SC route.

For the pre-dialysis CRF subjects of Study 202, the data suggest that ARANESP, administered weekly by SC injection at a starting dose of 0.45 μg/kg/week, corrects anemia as rapidly as EPO. In general, however, the ARANESP and EPO starting doses appeared excessive: doses of both study agents were titrated downwards during the study. Importantly, despite decreases in the doses of both agents, roughly two-thirds of subjects exceeded the upper limit of the Hgb target range (13 g/dL). Thus, for a pre-dialysis population, a starting dose of 0.45 μg/kg/week appears to be excessive.

Approximately three-quarters of the subjects became iron deficient at some point during the studies, highlighting the need for judicious iron supplementation.

For subjects who reached a Hgb concentration in excess of 14 g/dL, the median time required for Hgb to decline to <12 g/dL following discontinuation of study agent appears to be 6–8 weeks.

The mean rate of Hgb decease was ~0.33 g/dL per week. This was true for both ARANESP and EPO, and was true in both studies.

The studies provide moderate evidence of the safety of ARANESP in correcting anemia in the CRF patient population. The studies do not raise safety concerns, although the informativeness of the data is limited by the low numbers of subjects in the active control (EPO) groups, as well as the high background rate of AEs in these patient populations. The SAEs and AEs are reviewed comprehensively in CBER's integrated analysis of safety. No antibody formation was detected for any subject in either study.

Phase 3 Studies for Treatment of Anemia in Subjects Previously Maintained on EPO:

The North American Protocol 980117 and the European Protocol 970200 were the major phase 3 studies designed to show non-inferiority of ARANESP relative to EPO with respect to efficacy and safety. The studies were similar in their objectives, designs and patient populations, and are presented together in this review. Where appropriate, the studies are compared and contrasted. For the purpose of this review, protocols ARANESP 980117 and 970200 are referred to as Studies "117" and "200," respectively:

Study 117 – North American Phase 3 Study:

Title:	A Randomized Double-Blind, Non-Inferiority Study of IV ARANESP Compared to IV Recombinant Human Erythropoietin (EPO) for Treatment of Anemia in Patients with End-Stage Renal Disease (ESRD) Receiving Hemodialysis
Study Period:	July, 1998 – August, 1999
Centers:	Forty (40) centers: 35 centers in the U.S.; 5 centers in Canada
Subjects:	504 randomized
Note:	This study was conducted under IND -----.

Study 200 – European Phase 3 Study:

Title:	A Randomized, Comparative Study of ARANESP and Recombinant Human Erythropoietin for Prevention of Anemia in Subjects with Chronic Renal Failure Receiving Dialysis
Study Period:	October, 1997 – August, 1999
Centers:	Thirty-one (31) centers in Europe: 8 in the United Kingdom, 5 in Germany, 4 in Australia, 3 each in France and Sweden, and 2 each in Spain, The Netherlands, Austria, and Belgium
Subjects:	522 randomized
Note:	This study protocol was not conducted under IND.

Objectives:

The objectives of both studies were to show that ARANESP is not inferior to EPO for treatment of anemia in patients with ESRD receiving dialysis, and to compare the safety of the two agents.

Study Designs:

Study 117, the North American pivotal phase 3 study, was a randomized, double-blind, active control study of ARANESP versus EPO for the *maintenance* of Hgb in subjects with ESRD

receiving HD. Study 200, the European/Australian study, was similar in design, except that it was open-label, and subjects could be receiving HD or PD.

Subjects were to be on a stable regimen of EPO, with a baseline Hgb between 9.5–12.5 g/dL at the time of enrollment. In Study 200, subjects could be receiving Epoetin alfa or Epoetin beta at baseline, whereas Study 117 enrolled subjects on Epoetin alfa only. (Epoetin beta is not licensed in North America.) After 2-week screening and baseline periods, subjects were to be randomized 2:1 to ARANESP or EPO. Subjects assigned to EPO were to continue on their previous dose of EPO. Subjects assigned to ARANESP were to switch to ARANESP, at a total weekly starting dose that was based on the total weekly EPO dose at the time of randomization using the proportionality 1 μg ARANESP to 200 units EPO. Hgb was to be maintained within a target range of -1.0 to +1.5 g/dL of the baseline Hgb and between 9–13 g/dL for up to 28 weeks, with dose adjustments as needed per protocol-specified algorithms.

For Study 117, CBER requested and the sponsor included an entrance criterion requiring evidence of a 1-gram increase in Hgb in response to initiation of EPO. The rationale was to provide confirmation that the active comparator was having a therapeutic effect within the subject population studied. Study 200 did not include this provision.

In Study 117, the route of administration was exclusively IV, and all subjects were to receive blinded study agents on a thrice-weekly schedule (weekly ARANESP with biweekly placebo; or thrice-weekly EPO). In Study 200, the route of administration could be IV or SC, consistent with the pre-study route. Subjects receiving EPO on BIW or TIW schedules were to be changed to ARANESP on a weekly schedule, and subjects receiving weekly EPO were to be changed to ARANESP once every other week. In both studies, subjects assigned to EPO were to continue the agent using the pre-study dose, schedule and route of administration.

A period of 20 weeks (Study 117) or 24 weeks (Study 200) was to be allowed for dose-titration and stabilization of Hgb. Efficacy endpoints were assessed during a subsequent evaluation period of 8 weeks (Week 21–28, Study 117; Week 25–32, Study 200). For Study 117, an end-of-study evaluation was to be performed at Week 29. For Study 200, subjects were to continue for an additional 20-week maintenance period (weeks 33–52) for further safety comparisons.

Reviewer's Comments:
Study 117 was the only randomized, double-blind, clinical trial in the ARANESP clinical development program.

These studies were designed to assess the efficacy and safety of ARANESP in *maintaining* erythropoiesis in subjects who were receiving stable doses of EPO. The studies, therefore, had important limitations:

1. The studies do not directly support the efficacy of ARANESP for the proposed labeling claim (i.e., …treatment of *anemia* associated with CRF), because subjects in these studies were not anemic at baseline.
2. Initiation of erythropoietic therapies in anemic subjects may be associated with risks related to the increased hemodynamic burden imposed by an expanding extravascular volume, as well as theoretical risks related to increasing blood viscosity (i.e., HTN, seizures, TVA, etc.). By design, these studies did not address the safety of ARANESP in this context.

3. The studies were performed in selected patient populations, in that subjects could meet entrance criteria only if they had shown a stable response to EPO. Presumably, such subjects were more likely to respond predictably to ARANESP.
4. The pre-study maintenance EPO dose was used to calculate the starting dose of ARANESP. In clinical practice, however, such information would not be available for EPO-naïve patients.

Definitions of Terms:

Target Hgb Range: Hgb between 9.0 and 13.0 g/dL (inclusive) and within -1.0 to +1.5 g/dL (inclusive) of the baseline Hgb
Therapeutic Hgb Range: Hgb between 9.0 and 13.0 g/dL (inclusive)

Reviewer's Comment: The concept of a "therapeutic Hgb range" was not included in the original protocols, but was added through amendment.

Weekly Hgb Value: the mean of all Hgb values obtained during a single study week
Baseline EPO Dose: the total weekly EPO dose at time of randomization
Baseline Hgb Value: the mean of the 6 Hgb values obtained during the screening and baseline periods (2 from the screening period plus 4 from the baseline period)
Evaluation Hgb Value: the mean of the weekly Hgb values during the evaluation period (weeks 21–28)
Change in Hgb Between Screening/Baseline Period and Evaluation Period: evaluation Hgb value minus baseline Hgb value
Unstable Hgb Concentration During Evaluation Period: ≥ 2 consecutive weekly Hgb values during the evaluation period fulfilling any of the following criteria:

- < 9.0 g/dL or > 13.0 g/dL
- 1.0 g/dL below or > +1.5 g/dL above the baseline Hgb
- a single Hgb value < 8.0 or > 14.0 g/dL (confirmed at the next Hgb measurement)

Study Population:

The studies were to enroll clinically stable adult subjects with ESRD receiving HD (Study 117) or dialysis (HD or PD, Study 200), on a stable EPO dose.

Inclusion Criteria:

- age ≥ 18 years
- ESRD
    - on HD for ≥ 12 weeks (Study 117)
    - on HD or PD for ≥ 6 months (Study 200)
- clinically stable, no planned change in dialysis modality
- receiving a stable EPO regimen before enrollment into the study
    - EPO given TIW for 8 weeks by the IV route, with ≤ 25% change in dose (Study 117)
    - EPO given 1, 2, or 3 times weekly by either IV or SC route for 3 months, at the same prescribed dose, schedule and route of administration (Study 200)
- mean baseline Hgb of 9.5–12.5 g/dL
- no evidence of iron deficiency
    - transferrin saturation ≥ 20% (Study 117)
    - serum ferritin ≥ 100 μg/dL (Study 200)

- Study 117 only: documentation of a 1.0 g/dL increase in Hgb following initiation of EPO (to ensure that EPO had demonstrated efficacy in the enrolled subjects)

Exclusion Criteria:

- uncontrolled HTN
- advanced CHF (New York Heart Association Functional Class III-IV)
- grand-mal epilepsy
- RBC transfusions within 8 weeks
- severe hyperparathyroidism
- major surgery within 12 weeks (excluding vascular access surgery)
- clinical evidence of current systemic infection or inflammatory disease
- current active peritonitis (for subjects receiving PD in Study 200, only)
- ALT or AST > 2x the upper limit of the normal range
- current active liver disease; hepatitis B (Study 200, only)
- androgen therapy within 12 weeks
- RBC transfusions within 8 weeks (Study 117); within 1 month (Study 200)
- systemic hematological disease (e.g. sickle cell anemia, myelodysplastic syndromes, hematological malignancy, myeloma, hemolytic anemia)
- +HIV antibody
- clinical evidence of current malignancy (other than non-melanomatous skin malignancy)
- pregnant or breast feeding (women with child-bearing potential were to be using adequate contraceptive precautions)
- known hypersensitivity to human albumin (Study 117, only)
- scheduled for renal transplant - living related donor (Study 117, only)

Randomization and Treatments:

For both studies, subjects were planned to be randomized 2:1 to ARANESP or EPO.
Study 117: An unblinded pharmacist/designee contacted a central randomization system (an interactive voice response system [IVRS]) for assignment of study subject numbers. Randomization was stratified by center with two different block sizes per center. The unblinded pharmacist/designee was to pre-fill syringes with ARANESP, EPO and/or the appropriate volume of diluent. Intravenous injections were to be administered through the venous access during dialysis sessions.

Study 200: The investigator/designee contacted a central randomization system (IVRS) for assignment of study subject numbers (the study was open-label). Randomization was stratified by center and frequency of administration of EPO at study entry (1, 2, or 3 times weekly). Subcutaneous injections could be administered outside the dialysis center by medical staff, assistants, or the subject.

Dose Adjustments:

Doses of study drugs were to be adjusted to maintain Hgb within a target range of -1 to + 1.5 g/dL of baseline and between 9 and 13 g/dL. Dose changes were to have been made at beginning of next full dosing week, as follows:

- Increases in 25% increments of the starting dose for Hgb below target range; further increases only after 2 additional consecutive weekly Hgb values below target range
- Reductions in 25% increments of the starting dose for Hgb above target on 2 consecutive weekly determinations; further decreases only for 2 further consecutive weekly Hgb values

above the target range. (For Study 200, if a subject had 2 consecutive weekly Hgb determinations above the target Hgb range after a 75% decrease in dose, then the dosing frequency was to be reduced incrementally: TIW → BIW → QW → QOW.)
- Hgb was repeated at the next dialysis session for a value <8 or >14 at any time. For a confirmed the out-of-range value, the dose of study agent was to be adjusted and/or appropriate investigations and actions taken as clinically indicated.

Material Source:

ARANESP was provided in vials containing 1 mL of study drug for single-dose use only. Vials contained 20 or 100 μg (or 500 μg – Study 200) of ARANESP per mL. For Study 117, EPO vials contained 1 mL of study drug at a concentration of 10,000 U/mL. For Study 200, EPO comparators Eprex® (Epoetin alfa) or Recormon® (Epoetin beta) were formulated, packaged, labeled and stored according to local manufacturer, supplier, and institutional procedures, and were supplied by the study site pharmacy.

Screening Period:

Screening was to be performed within 2 weeks before baseline period. Screening included: medical history with current medications, physical examination, vital signs, height and weight (Study 117, only), 12-lead ECG (Study 117, only), CBC with differential leukocyte count, reticulocyte count, platelet count, serum chemistries, coagulation (Study 200, only), serum ferritin, serum iron, total iron binding capacity, transferrin saturation (Study 117, only), and Kt/V or URR (Study 117, only). (Kt/V is a unitless measure of the adequacy of HD, wherein K is the rate of urea clearance by the artificial kidney, t is the duration of dialysis, and V is the volume of distribution of urea. A value of 1.2 is the minimal recommended value. URR is the urea reduction ratio, the percent reduction in urea associated with dialysis [minimum recommended value is 65%].)

Baseline Period:

Baseline evaluations were to take place over a 2-week period, between the screening period and the dose titration period. Evaluations were to include vital signs, CBC and reticulocytes, twice weekly.

Dose Titration, Evaluation and Maintenance Periods:

Study 117 included a 20-week dose titration period, followed by an 8-week evaluation period (Weeks 21–28). Study 200 included a 24-week dose titration period, followed by an 8-week evaluation period (Weeks 25–32), and finally a 20 week maintenance period (Weeks 33–52). Monitoring was relatively consistent between these periods, except where noted below.

- AEs were monitored continuously
- CBC (with reticulocyte count – Study 117, only) weekly
- serum ferritin before initial dose of study agent, then monthly (Study 117); or weekly through the evaluation period, and then every 4 weeks thereafter (Study 200)
- serum iron, total iron-binding capacity, and transferrin % saturation, monthly (Study 117, only)
- biochemistry profile - before initial dose of study agent, and pre-dialysis at weeks 10, 20 (Study 117); or every 8 weeks (Study 200)
- trough ARANESP/EPO levels - before initial dose of study medication and at weeks 10 and 20 (Study 117); or every 4 weeks (Study 200)

- ARANESP/EPO antibodies - before initial dose of study medication and at weeks 10 and 20 (Study 117); or every 12 weeks (Study 200)
- Kt/V or URR evaluations and estimated dry weight during screening/baseline and at weeks 10 and 20 (Study 117, only)
- pre-dialysis BP – weekly

Completion/Termination:

Assessments included AEs, complete physical examination, vital signs, CBC, differential, platelets and reticulocytes, biochemistry profile, serum ferritin, transferrin saturation, antibody assays, changes to anti-hypertensive regimen and/or dialysis adequacy as assessed by Kt/V or URR, and PK troughs.

Two assays were developed to detect ARANESP antibodies: a ---------- screening assay to detect immunoreactivity to ARANESP or EPO, and a ---------- to detect antibodies that neutralize or inhibit the activity of ARANESP or EPO.

Response Variables:

Primary Efficacy Endpoint:

The primary efficacy endpoint was the change in Hgb from baseline through the Week 21 to 28 evaluation period. Based on the definitions of baseline Hgb and evaluation Hgb, this change can be expressed as:

$\Delta \equiv$ [mean of 8 Hgb values during Weeks 21 - 28] – [mean of 6 Hgb values during baseline].

The lower limit of the two-sided 95% confidence interval for the difference between mean change in Hgb on ARANESP vs. EPO was to be computed. This was to be adjusted for center and baseline Hgb using an analysis of covariance (ANCOVA). Treatment-by-center and treatment-by-baseline Hgb interaction effects were to be excluded from the ANCOVA model if the combined F-test was not statistically significant at the alpha=0.15 level. Otherwise, the non-significant interaction (at alpha=0.15) was to be excluded and significant interaction retained in the model. The homogeneity between baseline Hgb levels and across centers was to be assessed in subgroup analyses.

ARANESP was to be considered non-inferior to EPO if the lower limit of this confidence interval was above -1.0 g/dL. The unadjusted two-sided 95% CI was to be a 2° analysis.

Sample Size:

Both studies had planned sample sizes of 495 (330 ARANESP:165 EPO).
Study 117: Assuming that the largest clinically acceptable difference in the mean change in Hgb between the ARANESP and EPO groups was 1 g/dL, the sample size provided >90% power to demonstrate that ARANESP was not inferior to EPO.
Study 200: Assuming that the largest clinically acceptable difference in the mean change in Hgb between ARANESP and EPO groups was 0.5 g/dL, this sample size provided a power of >90% to demonstrate that ARANESP was not inferior to EPO.

Missing Data:

For the per-protocol (pP) analysis, there was to be no imputation for missing data. For the mITT analysis, missing data were to be imputed with ---------- software. Subgroup analyses were to be performed for descriptive purposes.

Secondary Efficacy Endpoints:

- instability of Hgb during the evaluation period, defined as percentage of subjects with:
  - ≥2 consecutive weekly Hgb values <9 or >13
  - ≥2 consecutive weekly Hgb values >1 g below or >1.5 g above baseline
  - a single value <8 or >14 confirmed by next Hgb measurement
- percentage of Hgb values within the target range during the evaluation period expressed as % of observations in evaluation period per patient
- percentage of Hgb values within the therapeutic range during the evaluation period expressed as % of observations in evaluation period per patient
- dose of study drug during the evaluation period - - weekly dose of study drug within evaluation period (total dose/weeks in period), to be summarized by treatment group, standardized by weight
- RBC transfusions during the evaluation period (Study 200, only)

Secondary Safety Endpoints:

- AEs, with those thought to be dialysis and non-dialysis related to be summarized separately. Hypertension, TVA, convulsions, cerebrovascular disorder, TIA and MI to be tabulated separately.
- Within-patient variances in Hgb levels during dose-titration and evaluation periods to be calculated from the residuals of the linear regression model (i.e., mean squared error [MSE]). For Study 117, these analyses were to be conducted over time intervals of Weeks 1–12, 13–20, 21–28, and 17–28 for each subject. For Study 200, these analyses were to be conducted over time intervals of Weeks 1–12, 13–20, 25–32 and 21–32. Individual subject variances were to be summarized by treatment group and time interval. The between-groups non-parametric comparison for the variance was to be presented at evaluation period. Patients with < 6 observations within a period were to be excluded for that period. Log-transformation was to be used to calculate 95% CI as an exploratory analysis.
- maximum rates of rise/decline (slope) in Hgb level during dose-titration and evaluation periods. For these analyses, regression lines were to be fitted over moving 4-week observation periods (4 weekly Hgb values), with determination of maximum rates of rise and decline in Hgb for each subject in the dose-titration and evaluation periods. An additional analysis was to be conducted over moving observation periods with 3 data points.
- numbers of dose adjustments by study week; aggregate numbers and proportion of subjects with ≥1 change were to be calculated separately for dose-titration and evaluation periods
- RBC transfusion by treatment period (dose-titration/evaluation periods), amount (none, 1 unit, or ≥ 2 units), and days with transfusions
- laboratory parameters (including ferritin and transferrin saturation, serum ARANESP and EPO levels, biochemistry & hematology parameters, BP measurements
- numbers and proportions of subjects who experienced iron deficiency
- numbers and proportions of subjects who developed antibodies to study agents
- For the safety analyses, the sponsor planned to calculate the variances from the residuals of the regression models, and then to log-transform them and summarize by group and time window.

Reviewer's Comments:

- Log-transformation tends to de-emphasize variability in the positive direction (relative to the negative direction). Moreover, the biological meaning of this log-transformed parameter is unknown. The sponsor was made aware of these concerns when the statistical analytic plan was discussed with the Agency.
- The sponsor's variance calculations were based on week, irrespective of the actual date of the test. Multiple values obtained during a single week were averaged.

Definitions of Evaluable Subsets:

For these non-inferiority studies, per-protocol analyses were used for the primary endpoints, comparing subjects according to actual treatment received. Modified intent to treat analyses were used for secondary efficacy analyses.

Per Protocol (pP) Analysis Set:

Subjects in the pP analysis set:

- had completed the dose-titration and evaluation periods
- had ≥ 6 Hgb measurements during the evaluation period
- had received the intended dose of study agent:
  - ≥ 75% of the total prescribed amount of study agent (U or μg) between weeks 17 and 24, inclusive, Study 117
  - received doses according to the protocol and within a ± 15% range, Study 200
- had not received RBC transfusions:
  - no receipt of > 1 unit RBCs between weeks 11 and 28, inclusive, Study 117
  - no transfusion of RBCs during weeks 15–32, Study 200
- had a consistent mode of dialysis and route of test agent administration until the completion of the evaluation period (Study 200, only)

Reviewer's Comment: Of note, the definition of pP does not take into account protocol entrance violations. Thus, subjects who violated inclusion/exclusion criteria were not excluded from the pP analysis set.

Modified Intent-To-Treat Analysis Set:

The mITT analysis set consisted of all randomized subjects who received ≥ 1 dose of study agent, and were analyzed by the group to which they were randomized.

Reviewer's Comment: Randomized subjects who received ≥1 dose of the study agent to which they were assigned do not constitute a modified ITT population. More properly, such subjects comprise a modified "as treated" population. However, for conformity with the sponsor's study report, the "mITT" acronym will be used in this review.

Safety Analysis Set:

The safety analysis set consisted of all subjects who received ≥ 1 dose of study agent. Subjects who received ≥ 1 dose of ARANESP were analyzed in the ARANESP group.

Study Administration:

Protocol Amendments

Study 117: There were 4 protocol amendments, dated June 9, 1998, August 11, 1998, October 26, 1998, and June 2, 1999. There were 2 changes that affected study conduct/analyses: The August 11, 1998 amendment added an inclusion criterion requiring evidence of an increase in Hgb concentration of >1.0 g/dL after initiation of EPO therapy. This criterion was implemented after discussions with the CBER, to obtain evidence that subjects enrolled in the study were actually receiving benefit from EPO. The June 2, 1999 amendment specified the use of ---------- software to impute missing data, and added a new Hgb range, defined as the "Therapeutic Range." This was to be defined as a Hgb of 9–13 g/dL, in contradistinction of the "Target Range," which had been defined as a Hgb 9–13 g/dL *and* within -1 to +1.5 g/dL of the baseline Hgb.

Study 200: There were 2 protocol amendments, dated October 28, 1997 and March 19, 1998. The first amendment directed that dose modifications be made after 2 (rather than 3) consecutive out-of-range Hgb values. Based on a decision to change the primary endpoint definition of non-inferiority from a one-sided 95% CI to a one-sided 97.5% CI (a two-sided 95% CI), the second amendment increased the sample size from 405 to 495 subjects. The amendment also proscribed RBC transfusion during the screening/baseline periods.

Changes in Statistical Analysis Plans:

The statistical analysis plan for Study 117 was modified 19 August 1999, prior to locking or unblinding the database. Substantive changes included a change in reporting AE rates between groups (from 95% CIs to Fisher's exact test, because of lower than expected event rates), and a formula for assigning a start date for an AE if none was recorded. The statistical analysis plan for Study 200 had existed in draft form, and the final plan, dated February 11, 1999, implemented changes to make the plan consistent with Study 117.

Interim Analyses:

For Study 117, an external Safety Monitoring Committee (SMC) reviewed safety data on two occasions; after the randomization of 100 and 300 subjects. For Study 200, a safety analysis was performed when all subjects had completed the evaluation period, and 100 subjects receiving ARANESP had completed 12 months on study. No interim analyses were conducted for efficacy in either study.

Results:

Enrollment and Disposition of Subjects:

After all subjects had been randomized in Study 117, the sponsor discovered that treatment group allocation had been inadvertently reversed by a contractor. Thus, study agent assignments were reversed for all subjects, such that subjects had been randomized to ARANESP and EPO in a 1:2 ratio, rather that in a 2:1 ratio, as planned. This error was communicated to the Agency on January 7, 1999. The sponsor made the point that the statistical power of this non-inferiority study would not be altered by the error. CBER agreed with the sponsor's arguments with respect to demonstration of non-inferiority on the primary endpoint, but stressed that the unintended reduction in the number of subjects randomized to ARANESP would importantly reduce the ARANESP safety database.

A total of 507 subjects were randomized into Study 117: 169 subjects were allocated to ARANESP and 338 continued with EPO. The first subject received study medication July 20, 1998; the last subject completed end-of-study assessments on August 2, 1999. For Study 200, there were 522 subjects randomized: 347 subjects were randomized to ARANESP; 175 remained on EPO. The first subject received study medication on November 11, 1997 and the last subject completed the end of study assessments on August 3, 1999.

A total of 40 centers (35 in the US and 5 in Canada) enrolled subjects in Study 117. Thirty-one centers participated in Study 200 (8 in the United Kingdom, 5 in Germany, 4 in Australia, 3 each in France and Sweden, and 2 each in Spain, the Netherlands, Austria and Belgium).

Three subjects randomized to remain on EPO in Study 117, and 3 subjects randomized to receive ARANESP in Study 200, did not receive study drug.

Discontinuations are summarized in Table 6. Eighty-five subjects did not complete Study 117, with discontinuations balanced between treatment arms (roughly 17% in each). For Study 200, discontinuations were more frequent in the ARANESP group (29.1% versus 18.3% for the ARANESP and EPO groups, respectively). Thus, over both studies combined, for which the numbers of subjects assigned to the ARANESP and EPO treatment groups was virtually the same (ARANESP: 516; EPO 513), rates of discontinuation were 25.0% for ARANESP and 17.3% for EPO.

Table 6: Disposition of Randomized Subjects by Study Period: Studies 117 and 200

	Study 117		Study 200	
	ARANESP	**EPO**	**ARANESP**	**EPO**
Randomized	169	338	347	175
Received Study Drug	169 (100%)	335 (99.1%)	344 (99.1%)	175 (100%)
Dose-Titration				
Started	169 (100%)	335 (99.1%)	344 (99.1%)	175 (100%)
Discontinued	17 (10.1%)	40 (11.8%)	42 (12.1%)	17 (9.7%)
Completed	152 (89.9%)	295 (87.3%)	302 (87.0%)	158 (90.3%)
Evaluation				
Started	152 (89.9%)	295 (87.3%)	302 (87.0%)	158 (90.3%)
Discontinued	9 (5.3%)	13 (3.8%)	13 (3.7%)	5 (2.9%)
Completed	143 (84.6%)	282 (83.4%)	289 (83.3%)	153 (87.4%)
Maintenance				
Started			289 (83.3%)	153 (87.4%)
Discontinued			43 (12.4%)	10 (5.7%)
Completed			246 (70.9%)	143 (81.7%)
End-of-Study Period				
Started	143 (84.6%)	282 (83.4%)		
Discontinued	2 (1.2%)	1 (0.3%)		
Completed	141 (83.4%)	281 (83.1%)		
Total Discontinued	28 (16.6%)	57 (16.9%)	101 (29.1%)	32 (18.3%)
Total Completed	141 (83.4%)	281 (83.1%)	246 (70.9%)	143 (81.7%)

For the combined studies, the chief reasons for discontinuation were death, kidney transplant, intolerable AEs, and withdrawal requested (Table 7). In Study 200, a difference in mortality was apparent, with death reported in 10.1% of ARANESP-treated subjects and 5.7% of EPO-treated subjects. In Study 117, the respective rates of death were 4.7% and 5.9%. In blinded Study 117, discontinuations due to intolerable AEs were reported in 3.6% and 5.0% of ARANESP and EPO-treated subjects, respectively. For Study 200 (open-label), discontinuations due to intolerable AEs were reported in 3.5% and 1.7% of subjects in ARANESP and EPO-treated subjects, respectively.

Table 7: Reasons for Discontinuation of All Randomized Subjects: Studies 117 and 200

	Study 117		Study 200	
	ARANESP	**EPO**	**ARANESP**	**EPO**
Number of Subjects	169	338	347	175
Subjects Not Receiving Study Agent	0 (0%)	1 (0.3%)	1 (0.3%)	0 (0%)
Withdrawals in Subjects Receiving Study Agents				
Death on Study	8 (4.7%)	20 (5.9%)	35 (10.1%)	10 (5.7%)
Kidney Transplant	8 (4.7%)	7 (2.1%)	27 (7.8%)	14 (8%)
Intolerable AE	6 (3.6%)	17 (5%)	12 (3.5%)	3 (1.7%)
Withdrawal Requested	4 (2.4%)	7 (2.1%)	14 (4%)	3 (1.7%)
Administrative Decision	0 (0%)	2 (0.6%)	6 (1.7%)	0 (0%)
Lost to Follow-up	1 (0.6%)	0 (0%)	3 (0.9%)	1 (0.6%)
Protocol Violation	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)
Change in Dialysis Modality	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)

In each study, there were 3 subjects excluded from the mITT analyses because of failure to receive a dose of a study agent. Thus, across both studies, the mITT population included 99.4% of all randomized subjects. In Study 117, ~72% of subjects were evaluable for the per-protocol analyses, with reasons for non-evaluability balanced across study groups. For per-protocol analyses In Study 200, ~65% of subjects were evaluable. Again, reasons for non-evaluability were balanced across study groups. The chief reason for a greater proportion of non-evaluable subjects in Study 200 was the use of doses outside of the prescribed range.

Subject Analysis Sets:

The numbers of subjects in each analysis set and the reasons for exclusion are summarized in Table 8. The percentages of per protocol evaluable subjects and the reasons for non-evaluability were similar within both studies. Failure to complete the evaluation period was the most common reason for exclusion from the per protocol analysis sets.

Table 8: Analysis Sets: Studies 117 and 200

	Study 117		Study 200	
	ARANESP	EPO	ARANESP	EPO
Number of Subjects	169	338	347	175
Randomized	169 (100%)	338 (100%)	347 (100%)	175 (100%)
ITT Analysis				
Evaluable	169 (100%)	335 (99%)	344 (99%)	175 (100%)
No study Medication	0 (0%)	3 (1%)	3 (1%)	0 (0%)
Per-protocol Analyses				
Evaluable	121 (72%)	240 (71%)	224 (65%)	112 (64%)
Non-Evaluable	48 (28%)	98 (29%)	123 (35%)	63 (36%)
No study Medication			3 (1%)	0 (0%)
Patient did not complete	30 (18%)	58 (17%)	56 (16%)	22 (13%)
RBC transfusions	7 (4%)	21 (6%)	22 (6%)	10 (6%)
Dose changes not per-protocol			36 (10%)	28 (16%)
Doses outside required range			2 (1%)	2 (1%)
Received <75% prescribed dose, weeks 17-24	10 (6%)	16 (5%)		
Change in route of administration			1 (0%)	1 (1%)
Change in mode of dialysis			2 (1%)	0 (0%)
< 6 Hgb assessments	1 (1%)	3 (1%)	1 (0%)	0 (0%)
Safety Analyses				
Evaluable	141 (83.4%)	281 (83.1%)	346 (99%)	173 (100%)
No study Medication	0 (0%)	3 (1%)	3 (1%)	0 (0%)

Protocol Violations and Errors:

Eligibility Violations:

Twenty percent (20%) of subjects violated inclusion or exclusion criteria in Study 117: 15.4% of subjects in the ARANESP group and 22.2% of subjects in the EPO group. Roughly half of these violations were for EPO dose changes greater than 25% in the 8 weeks preceding the study. Twenty subjects (3.0% ARANESP; 4.4% EPO) failed to meet baseline/ screening Hgb requirements on the basis of fewer than 6 baseline assessments or out-of-range values; however, only one subject had a mean baseline Hgb value that was actually out of range (12.6 g/dL). There were 15 subjects (3% in each group) lacking documentation of a $\geq$ 1.0 g/dL increase in Hgb in response to initiation of EPO therapy. Two subjects (1%) in the ARANESP group and 13 (4%) in the EPO group had diastolic hypertension. Violations of exclusion criteria included 1 ARANESP subject who received an RBC transfusion pre-study, 1 EPO subject with a malignancy, and 1 EPO subject with major surgery.

For Study 200, there were 32 protocol entrance criteria violations: 19 ARANESP (5.5%); 13 EPO (7.4%). Thirteen (13) subjects (3.7%) in the ARANESP group and 10 (5.7%) in the EPO group had changes to their EPO dose, frequency, or route within 3 months before study entry. Other violations of inclusion criteria included lack of a diagnosis of ESRD on dialysis for 6 months (2 EPO), and lack of documentation of serum ferritin >100 ng/mL (1 ARANESP; 1 EPO). There were 6 violations of exclusion criteria: 5 in the ARANESP group (1 each: HTN, RBC transfusions prior to study, HIV/positive hepatitis serology, and participation in another trial) and 1 in the EPO group (malignancy).

Incorrect Study Agent:

In Study 117, 26 subjects in the ARANESP group (15%) and 38 in the EPO group (11%) received 135 doses of commercial EPO. Forty-five of these subjects received incorrect study drug once and 19 subjects received incorrect study drug more than once. The administration of incorrect study drug peaked during the months when subject enrollment was highest. During the evaluation period, 11 subjects received a total of 17 doses of commercial EPO. No subjects in Study 200 were reported as having received the incorrect study agent.

Randomization Errors:

No randomization errors were reported in Study 117. Randomization in Study 200 was stratified by center and frequency of EPO administration at study entry. Seven (7) subjects were assigned treatment from the incorrect frequency of EPO strata (1 ARANESP, 6 EPO). These subjects remained on the study agent to which they were assigned; however, the 6 subjects who were assigned to EPO continued their EPO therapy at their frequency of EPO administration before study entry. The incorrect frequency assignment did not affect the ARANESP subject.

Missing Hemoglobin Values:

Four subjects in Study 117 were reported to have major protocol violations for <6 Hgb assessments during the evaluation period (1 ARANESP, 3 EPO). There were also major protocol violations for no Hgb assessment within 21 days for 2 subjects in the ARANESP group and 3 subjects in the EPO group.

In Study 200, 8 ARANESP subjects (2%) and 7 EPO subjects (4%) did not have Hgb assessments for 2 consecutive weeks during the titration period.

Iron Administration:

Sixteen subjects (13 ARANESP, 3 EPO) in Study 200 did not receive IV iron administration after 4 consecutive ferritin values <100 ng/mL: 12 subjects during the dose-titration period, 3 subjects during the evaluation period and 1 subject during the maintenance period.

Reviewer's Comment: Protocol violations and errors were generally minor, and would not be expected to importantly affect study results.

Demographics and Baseline Renal Disease Characteristics:

Within Study 117, the ARANESP and EPO groups were well-matched with respect to gender and race (Table 9). Overall, mean age was 58 years (range: 20–90). Fifty-six percent (56%) of the subjects were male, 42% were Caucasian, 39% were Black, and 8% were Hispanic. Relative to the EPO group, the ARANESP group tended to be slightly younger, with ~9% excess subjects in the 20–65 year-old age range, and ~9% fewer subjects in the 65 and older range. The proportions of subjects 75 and older was 14% in both groups. Mean dry weight was 78 kg (range: 35–188), and similar in both groups.

For Study 200, subjects were also well-balanced with respect to gender and race. Similar to the North American Study, 55% of the subjects were male; however, in contradistinction to the North American study, >90% of subjects were Caucasian in the European study. Age and weight were well-balanced between treatment groups. Relative to the population in the North American study (Study 117), these subjects were slightly older (difference of means = 2.4 years) and appreciably lower in weight (difference in mean dry weight ~9 kg). Of the 175 subjects randomized to EPO, 31 subjects (~18%) received Epoetin beta and the balance received Epoetin alfa.

Reviewer's Comments: Of the 516 subjects randomized to ARANESP across both studies, only

Table 9: Baseline Demographics: Studies 117 and 200

	Study 117		Study 200	
	ARANESP	**EPO**	**ARANESP**	**EPO**
Number	169	338	347	175
Gender (n, %)				
Male	94 (56%)	191 (57%)	188 (54%)	100 (57%)
Female	75 (44%)	147 (43%)	159 (46%)	75 (43%)
Race (n, %)				
Caucasian	68 (40%)	144 (43%)	316 (91%)	165 (94%)
Black	69 (41%)	129 (38%)	11 (3%)	5 (3%)
Hispanic	13 (8%)	29 (9%)		
Asian	13 (8%)	26 (8%)	18 (5%)	5 (3%)
Native American	2 (1%)	4 (1%)		
Other	4 (2%)	6 (2%)	2 (1%)	0 (0%)
Age (years)				
Mean	58.0	57.8	60.1	60.9
Median	60.0	59.5	63.0	63.0
SD	13.9	15.7	14.5	14.1
Quartiles	48 - 68	47 - 70	50 - 71	52 - 71
Range	20 - 86	21 - 90	18 - 88	22 - 87
Age (n, %)				
< 65	117 (69%)	204 (60%)	192 (55%)	97 (55%)
≥ 65	52 (31%)	134 (40%)	155 (45%)	78 (45%)
≥ 75	24 (14%)	46 (14%)	47 (14%)	28 (16%)
Dry Weight (kg)				
Mean	78.0	77.3	68.4	69.0
Median	78.0	74.0	68.0	67.5
SD	18.9	22.5	14.0	16.8
Quartiles	65 - 88	62 - 89	59 - 76	58.5 - 77
Range	43 - 141	35 - 188	32 - 123	38 - 184
Actual Weight (kg)				
Mean	80.9	80.2		
Median	80.4	77.0		
SD	19.4	22.9		
Quartiles	66 - 91.4	64 - 92.8		
Range	43.7 - 141	38 - 189		

80 (15.5%) were of African descent. The limited experience in these subjects was related, in part, to the randomization error (based on the demographics of Study 117, ~30% of total ARANESP-treated subjects would have been of African descent, if not for the randomization error). Given that nearly half of the U.S. target patient population is of African descent, the limited safety experience gained in this patient population is of some concern.

In Study 117, the most common causes of ESRD were diabetes mellitus, HTN, glomerulonephritis and polycystic disease (Table 10), with similar proportions between treatment groups. The mean time since onset of ESRD was 75 months (range 4–651), and subjects had been receiving HD for a mean of ~50 months (range 4–325).

Table 10: Baseline Renal Disease Status: Studies 117 and 200

	Study 117		Study 200	
	NESP	**EPO**	**NESP**	**EPO**
Number	169	338	347	175
Cause of Renal Failure (n, %)				
Diabetes	62 (37%)	116 (34%)	58 (17%)	18 (10%)
Hypertension	44 (26%)	88 (26%)	27 (8%)	13 (7%)
Glomerulonephritis	18 (11%)	36 (11%)	66 (19%)	36 (21%)
Polycystic disease	9 (5%)	16 (5%)	30 (9%)	14 (8%)
Other urologic	2 (1%)	5 (1%)	29 (8%)	14 (8%)
Other cause	26 (15%)	65 (19%)	73 (21%)	54 (31%)
Unknown	8 (5%)	12 (4%)	64 (18%)	26 (15%)
Mode of Dialysis (n, %)				
HD	169 (100%)	338 (100%)	318 (92%)	163 (93%)
PD	0 (0%)	0 (0%)	29 (8%)	12 (7%)
Type of Access (n, %)				
Natural fistula	70 (41%)	127 (38%)		
Graft	88 (52%)	176 (52%)		
Permanent catheter	10 (6%)	26 (8%)		
Other	1 (1%)	9 (3%)		
Time Since Onset of Renal Failure (Months)				
Mean	78	73.6		
Median	50	48		
SD	76.7	75.7		
Quartiles	31 - 106	27 - 89.5		
Range	4 - 496	5 - 651		
Time Since First Dialysis (Months)				
Mean	52.9	49.2	50.7	57.0
Median	34.5	33	32.0	36.7
SD	56.7	47.7	55.9	62.5
Quartiles	16.5 - 62	16.0 - 64	18.5 - 55.5	19.3 - 63.6
Range	4 - 325	4 - 267	7 - 321	6 - 335

For Study 200, the groups were well balanced with respect to baseline renal status. The most common reported etiology of ESRD was “other cause,” a category that included analgesic/ drug-

related nephropathy, nephritis from other causes, and renovascular conditions. Other leading reported causes included glomerulonephritis and diabetes. The mean time since first dialysis was 53 months (range 6 – 335), with 92% of the subjects receiving HD and 8% PD.

Reviewer's Comment: Thus, although Study 200 allowed enrollment of subjects receiving either HD or PD, the vast majority of subjects were receiving HD. Over both studies, therefore, only a slim minority of subjects were receiving PD (4%).

Concomitant Medical Conditions:

In Study 117, the prevalence of concomitant medical illnesses was well-balanced between treatment groups (data not shown). The most-frequent concomitant medical conditions included hypertension (96%), diabetes mellitus (46%), coronary artery disease (35%), peripheral vascular disease (26%), previous myocardial infarction (18%), and previous cerebrovascular events (16%). Forty-seven percent (47%) of subjects had a prior history of thrombosis of vascular access.

In Study 200, most common concomitant medical illnesses included hypertension (84%), diabetes mellitus (21%), peripheral vascular disease (20%), myocardial infarction (13%), and prior cerebrovascular events (11%). A history of thrombosis of vascular access was reported in 24% of subjects. There were no notable differences in associated medical illnesses between treatment groups (data not shown).

Baseline Hemoglobin, Iron Status and EPO Dose:

For both Studies, the ARANESP and EPO groups were well balanced with respect to baseline Hgb. Of note, the mean baseline Hgb was slightly higher in the North American study than in the European study (by ~0.2 g/dL, Table 11).

Serum ferritin was similar in the two treatment groups in Study 117, but tended to be slightly lower in the EPO group in Study 200. Transferrin saturation, reported in Study 117 only, was similar in both treatment groups (Table 11).

For Study 117, the median total weekly EPO dose at baseline was 12,000 Units/week (range: 1200 – 120,000; 10,500 Units/week in the ARANESP group and 12,000 Units/week in the EPO group. On a weight-adjusted basis, the median weekly EPO doses were 142 and 155 Units/kg/week in the ARANESP and EPO groups, respectively. In Study 200, the median baseline EPO dose in Study 200 was substantially lower – 6000 Units/week in both treatment groups (range: 500 – 30,000). The median weight-adjusted baseline EPO doses were 92.3 and 91.4 Units/kg/week in the ARANESP and EPO groups, respectively. Of note, the proportions of subjects receiving EPO on once-, twice-, and thrice-weekly schedules at baseline were 19%, 34%, and 47%, respectively, and these proportions were similar in both treatment groups.

Table 11: Baseline Hemoglobin and Iron Parameters: Studies 117 and 200

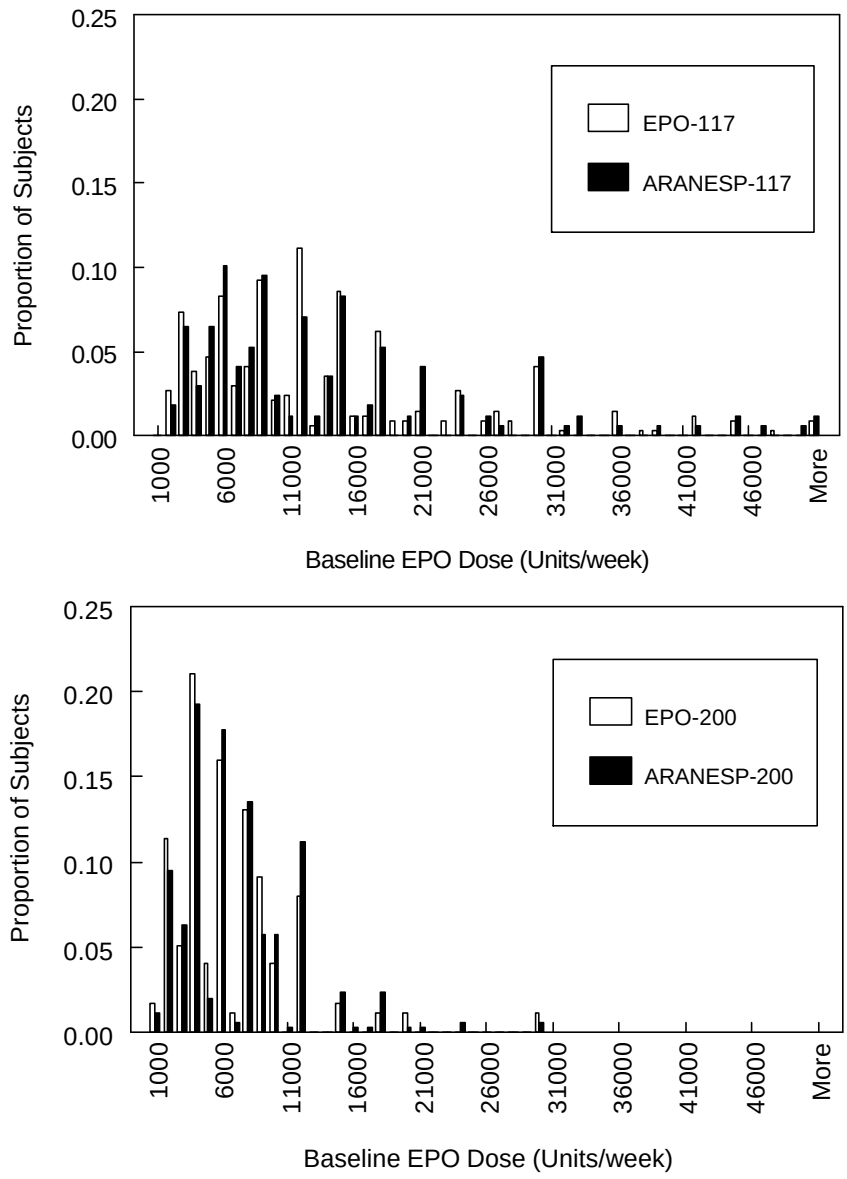
	Study 117		Study 200	
	ARANESP	**EPO**	**ARANESP**	**EPO**
Number	169	338	347	175
Hemoglobin (n, %)				
Level 1: ≤ 10.3 g/dL	18 (11%)	41 (12%)	79 (23%)	38 (22%)
Level 2: > 10.3-11.5 g/dL	97 (57%)	169 (50%)	171 (49%)	89 (51%)
Level 3: > 11.5 g/dL	54 (32%)	128 (38%)	97 (28%)	48 (27%)
Hemoglobin (g/dL)				
Mean	11.15	11.22	11.02	11.00
Median	11.18	11.22	11.00	11.00
SD	0.64	0.69	0.74	0.70
Quartiles	10.67 - 11.62	10.72 - 11.82	10.4 - 11.6	10.5 - 11.6
Range	9.7 - 12.5	9.6 - 12.6	9.5 - 12.5	9.5 - 12.5
Serum Ferritin (ng/mL)				
Mean	411	425	413	386
Median	375	371	319	287
SD	288	317	306	289
Quartiles	190 - 535	193 - 553	199 - 517	185 - 488
Range	16 - 1791	18 - 1913	96 - 1814	100 - 1493
Transferrin Saturation (%)				
Mean	32.8	32.1		
Median	28.8	29.2		
SD	12.3	11.6		
Quartiles	24.1 - 37.3	24.2 - 36.4		
Range	20 - 85	16 - 92		

Although the weight-adjusted baseline EPO doses were ~40% lower in Study 200 than in Study 117, there was good balance between the treatment groups within both studies. Figure 4 summarizes the distributions of baseline EPO doses with *x*-axes aligned, highlighting the differences in baseline EPO doses between the North American and European studies.

Reviewer's Comments: The median baseline EPO dose in the European study (Study 200) was roughly half that of the North American study (Study 117). Potential explanations for this striking disparity between North America and Europe/Australia include the following:

1. Greater body mass of North American subjects. Though subject weight tended to be greater in the North American study, ~14% higher, presumably this difference would not be sufficient to account for a 2-fold difference in median baseline EPO dose.
2. A goal of achieving a higher Hgb target in North America. Baseline Hgb was roughly 0.2 g/dL higher in the North American study. Again, this difference is directionally consistent with the disparity in baseline EPO doses, but is a relatively small difference that would not appear to be adequate to explain the large inequality in dose.

Figure 4: Distributions of Baseline EPO Doses: Studies 117 (Top) and 200 (Bottom)



3. Longer duration of CRF in North America. Presumably, with greater chronicity of disease, there are lower endogenous EPO levels and greater requirements for exogenous EPO. The studies were similar, however, in the interval since first dialysis (Table 10).
4. Lower iron stores in North American subjects. The data, however, do not bear out this hypothesis, in that baseline iron stores tended to be slightly greater in Study 117 than in Study 200.
5. Differing practice patterns between North America and Europe. For example, relative to practice patterns in Europe, there may be more reluctance to utilize RBC transfusions to maintain

Hgb in North America. (In support of this concept, there were, in fact, more RBC transfusions in Study 200 than in Study 117).

6. Given that the EPO dose-response relation is non-linear (i.e., diminished erythropoietic effect per unit mass at higher doses), substantial increases in EPO dosage towards the upper end of the dosing range could have a relatively small effect on Hgb. Thus, some North American physicians may be administering substantially more EPO than necessary to support erythropoiesis.

There appears to be no singular explanation for the large disparity in baseline EPO doses between studies, and it may be reasonable to attribute the difference to a combination a factors: differences in patient weight and baseline Hgb, diversity in clinical practice patterns, and the non-linearity of the EPO dose-response relation.

Starting ARANESP Dose:

The starting median weekly ARANESP dose in Study 117 was 0.68 μg/kg/week. For Study 200, the initial median weekly ARANESP dose was 0.50 μg/kg/week. This difference is a reflection of the difference in baseline EPO doses, as above.

Primary Efficacy Endpoint:

Δ Hgb - Baseline Through Evaluation Period

Study 117: The mean weekly Hgb values (±1 SD) from baseline through the titration and evaluation periods are shown for the per protocol dataset in Figure 5. Whereas the Hgb versus time relation was relatively flat for the EPO group, a rise in Hgb was observed in the ARANESP group during the dose-titration period, with a maximum mean difference of 0.36 g/dL observed on Weeks 13, 14, and 15. The mean Hgb decreased in the ARANESP group after Week 13, such that the mean weekly Hgb values for the two groups converged prior to the evaluation period. The maximum difference during the evaluation period was of 0.18 g/dL on Week 22. The SDs for each treatment group at baseline tended to be less than the SDs for weeks 2 through 28, presumably because study entrance criteria *mandated* a baseline Hgb within the range 9.5 – 12.5 g/dL, the variability of the baseline Hgb was limited because it represented the mean of several values, and because the target Hgb range was, in fact, a target, and the range of 9.0 to 13.0 g/dL was broader that the mandatory baseline range.

The distributions of changes in Hgb from baseline through the evaluation period were similar for the 2 treatment groups (Figure 6). The prospectively-defined primary efficacy endpoint, the mean change in Hgb for the pP population, adjusted for center and baseline Hgb concentration, was similar in the ARANESP and EPO groups: 0.24 ± 0.10 g/dL versus 0.11 ± 0.07 g/dL (mean ± SEM), respectively. The difference between groups was 0.13 g/dL (95% CI: -0.08, 0.33). The lower boundary of the 2-sided 95% CI was above the protocol-specified non-inferiority margin of -1.0 g/dL, providing support that ARANESP was not inferior to EPO in maintaining Hgb in this study. The analysis on the unadjusted mean change was consistent with the primary analysis. Covariate-adjusted and unadjusted analyses on the modified ITT data analysis sets, using 4 different methods to handle missing data, were also consistent with the pP analyses. The sponsor found consistent results for across gender, race, age, baseline Hgb concentration, baseline EPO dose, and center subgroups, with no significant treatment-by-center interactions. The results of sensitivity analyses, in which centers were treated as random effects and smaller centers were combined with larger centers based on geographic proximity, were consistent with other analyses.

Figure 5: Mean (± SD) Hgb by Study Week Per–Protocol Dataset – Study 117

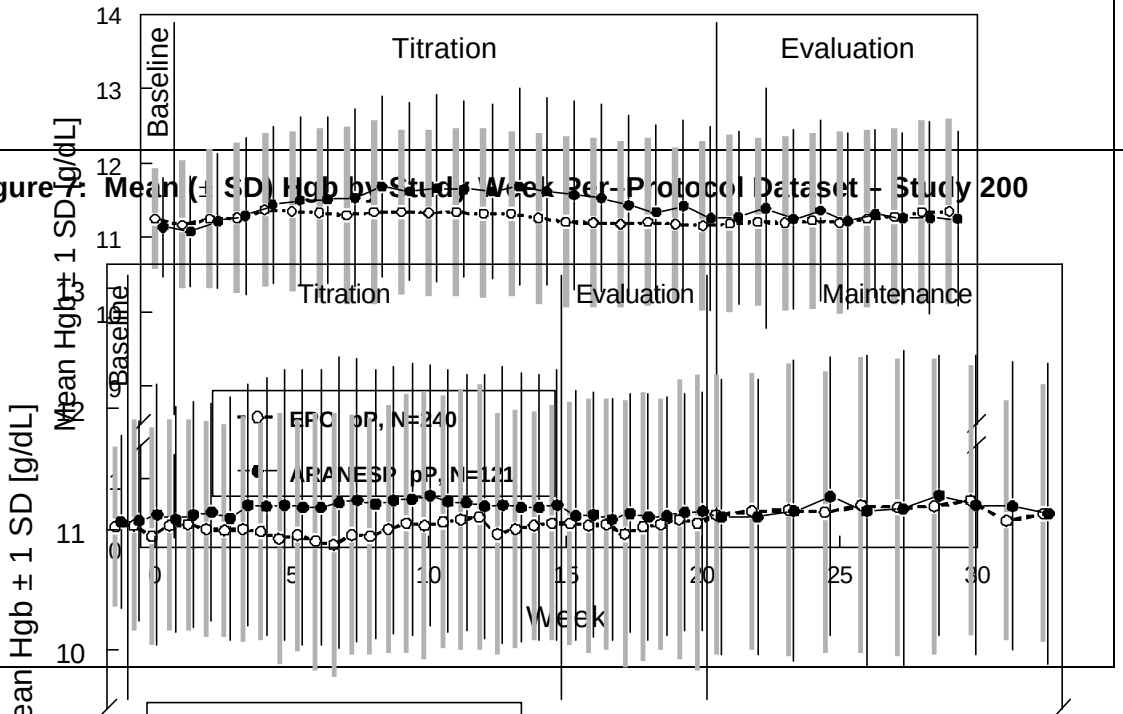
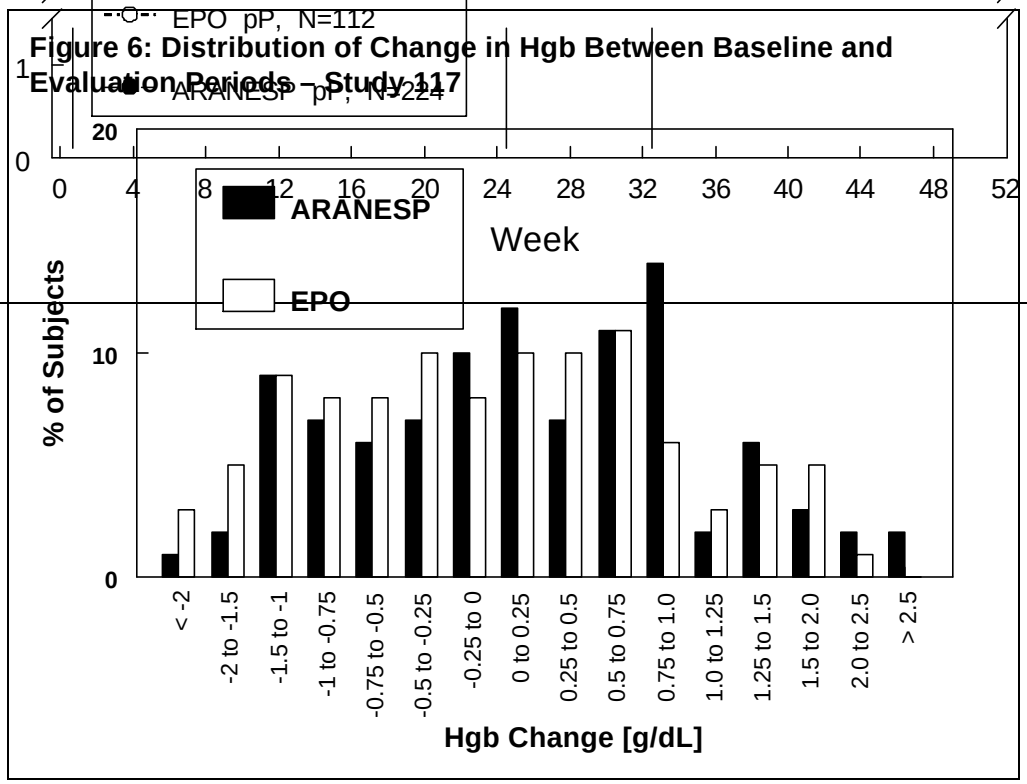


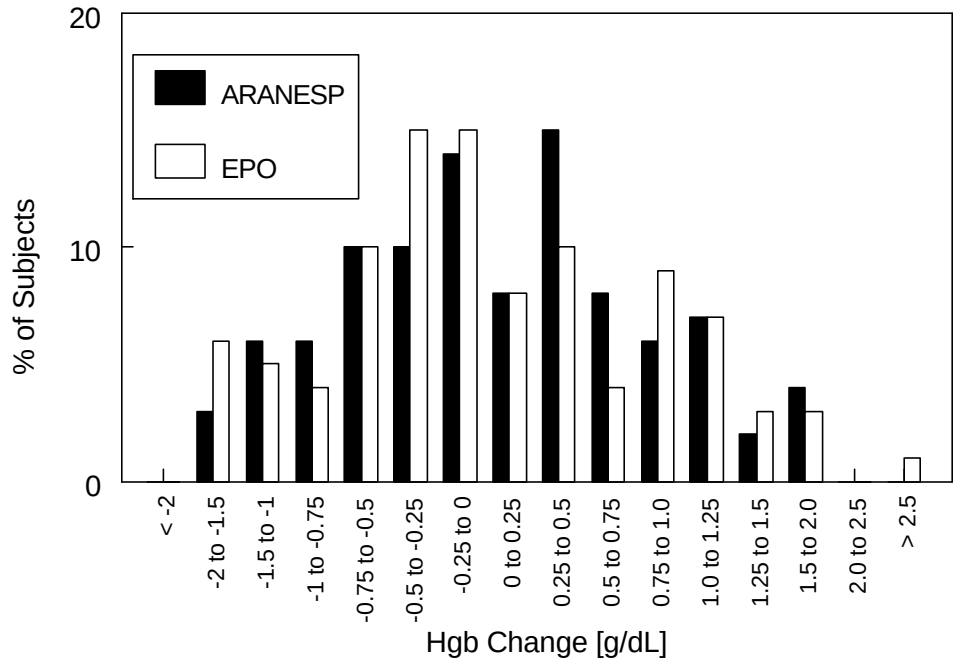
Figure 7: Mean (± SD) Hgb by Study Week Per-Protocol Dataset – Study 200

Figure 6: Distribution of Change in Hgb Between Baseline and Evaluation Periods – Study 117



Study 200: The mean weekly Hgb (± 1 SD) from baseline through the titration, evaluation, and maintenance periods are shown for the pP dataset in Figure 7. For the ARANESP group, the

Figure 8: Distribution of Change in Hgb Between Baseline and Evaluation Periods – Study 200



relation between mean Hgb and time was slightly uprising in the titration period, and relatively flat during the evaluation and maintenance periods. For the EPO group, the relation was very slightly downsloping in the first portion of the titration period, upsloping in the second portion of the titration period, and then fairly stable. The maximum difference in mean Hgb values was 0.35 g/dL, occurring on Week 12.

The change (mean ± SD) in Hgb from baseline to the evaluation period was similar in the ARANESP and EPO groups (0.05 ± 0.80 versus 0.00 ± 0.87 g/dL, respectively). After adjustment for covariates (center, frequency of EPO dosing at baseline, modality of dialysis, route of administration, and baseline Hgb concentration), the difference in the mean change in Hgb between the 2 groups was 0.03 g/dL (95% CI: -0.16, 0.21). The lower limit of the 2-sided 95% CI was above the protocol-specified non-inferiority margin of -0.5 g/dL, providing support that ARANESP was not inferior to EPO in maintaining the mean Hgb concentration in this study.

Results were consistent for subgroup analyses based on center, baseline Hgb concentration, EPO dose, baseline route and frequency of EPO administration, modality of dialysis, age, gender and race. No significant treatment-by-center interactions in either the pP or modified ITT analyses were observed, suggesting consistency of results across centers.

The distributions for the changes in Hgb between the baseline and evaluation periods were similar for the two treatment groups (Figure 8).

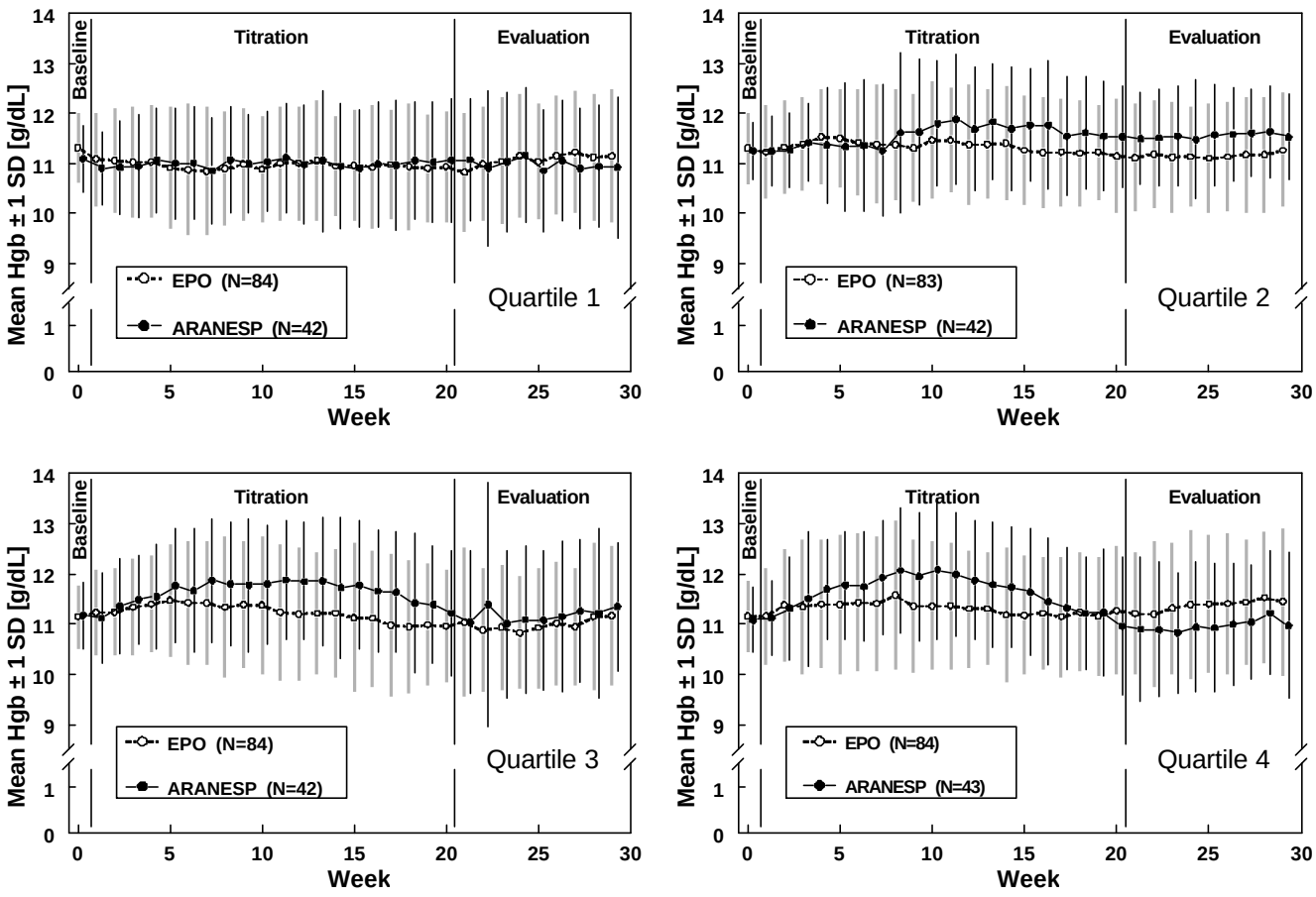
CBER Exploratory Analyses on the Primary Endpoints (Studies 117 and 200):

CBER analyzed the Hgb-time relations for the following subgroups of Studies 117 and 200:

1. age (<65, ≥65, ≥75)
2. gender (male, female)
3. race (Caucasian, Black, Hispanic [Study 117], "other" [Study 200])
4. weight (by quartiles)
5. etiology of CRF (diabetes, HTN, glomerulonephritis, polycystic disease, urologic, "other")
6. dialysis duration (by quartiles)
7. baseline Hgb (by quartiles)
8. previous EPO dose (by quartiles)
9. weight-adjusted dose at baseline (by quartiles)
10. study site (U.S. versus Canada [Study 117, only])

With 2 exceptions, the Hgb-time relations were generally consistent between these subgroups for both agents, and plots of Hgb versus time relations for these sub-groups are not shown. In Study 117, the general trend observed in the ARANESP group over the entire study population (i.e., mean Hgb values rising during the dose-titration period, peaking around Week 13, and converging with the EPO group prior to the evaluation period) was particularly evident in the lower weight quartiles (data not shown) and higher weight-adjusted dose quartiles (Figure 9, quartiles 3 and 4, bottom left and right panels). Conversely, for subjects in the lowest weight-adjusted dose quartile (Figure 9, left upper panel), the Hgb-time relation for ARANESP had a slope of essentially zero, and was virtually superimposable on the EPO group data. Thus, the general increase in Hgb values observed in the ARANESP group during the titration period appears to have been driven by subjects with higher weight-adjusted doses. For these subjects, therefore, the proportionality for substitution of ARANESP for EPO was, on the whole, excessive, suggesting non-linearity of the EPO → ARANESP conversion factor.

Figure 9: Hgb–Time Relation by Baseline Weight-Adjusted Dose Quartiles – Study 117



EPO: quartile 1 ≤ 80.4; quartile 2 >80.4 to ≤154; quartile 3 >154 to ≤234; quartile 4 >234 units/kg/wk
ARANESP: quartile 1 ≤ 84.9; quartile 2 >84.9 to ≤142; quartile 3 >142 to ≤227; quartile 4 >227 units/kg/wk

Secondary Efficacy Endpoints:

Instability of Hgb During the Evaluation Period:

Study 117: The proportions of subjects with unstable Hgb values during the evaluation period were similar in the two treatment groups: 42 subjects in the ARANESP group (35%), versus 90 subjects in the EPO group (38%). The proportions of subjects with unstable Hgb values were consistent between treatment groups for the sponsor's exploratory and sensitivity analyses. These included analyses on the modified ITT population with different methods for imputation of missing data, and sensitivity analyses using alternate definitions of unstable Hgb values. Results were also similar for subgroup analyses assessing baseline EPO dose quintiles and baseline Hgb groups (Hgb ≤10.3, >10.3–11.5, >11.5 g/dL). Unstable Hgb values tended to be more frequent in

subjects in the highest Hgb range, though there was no apparent difference between treatment groups.

Study 200: Fifty-four (54) subjects (24%) in the ARANESP group and 32 subjects (29%) in the EPO group experienced unstable Hgb values during the evaluation period. The results were similar when no adjustments were made for covariates, and similar for the modified ITT analyses. Subgroup analyses for modality of dialysis, frequency of EPO administration at study entry, initial EPO dose, route of EPO administration at study entry, and baseline Hgb did not suggest differences between treatment groups, though many of the subsets were quite limited in size, precluding definitive conclusions.

Reviewer's Comments: It is noteworthy that one-forth to one-third of subjects in both treatment groups in both studies exhibited unstable Hgb values during the evaluation period, despite the fact that this period followed a prolonged period for dose titration. The high frequency of unstable Hgb values suggests that the definition of "unstable" was not overly restrictive and therefore insensitive, in which case a lack of a disparity between groups would not have been as informative. The lack of a difference between groups suggests that ARANESP is similar to EPO in its performance characteristics; however, the large numbers of subjects with unstable Hgb values underscores the importance of judicious patient monitoring on a continuing basis.

Percentage of Hgb Values Within the Target Range During the Evaluation Period:

Study 117: For the pP analysis, the mean percentages of Hgb values within the target range were 76% and 72% in the ARANESP and EPO groups, respectively. Using the modified ITT analysis without imputation for missing values, 70% of values were in the target range in both treatment groups.

Study 200: For the pP analysis, 83% and 82% of Hgb values were within the target range in the ARANESP and EPO groups, respectively. For the modified ITT analyses, the proportions of Hgb values within the target range were also similar (76% in each group).

Percentage of Hgb Values Within the Therapeutic Range During the Evaluation Period:

Study 117: For the pP analysis, 91% of Hgb values in each treatment group were within the therapeutic range (9–13 g/dL) during the evaluation period.

Study 200: For the pP analysis, the mean percentages of Hgb values within the therapeutic range were 96% and 93% for the ARANESP and EPO groups, respectively.

Weekly Dose of Study Agent During the Evaluation Period:

Study 117: For ARANESP-treated subjects, the median ARANESP dose during the evaluation period was 38 μg/week, or 0.53 μg/kg/week on a weight-adjusted basis. This represents a decrease in dose relative to the starting dose (median 46 μg/week, 0.68 μg/kg/week). The dose reduction is consistent with the Hgb-time relation for ARANESP-treated subjects (Figure 5), showing trends towards increasing then decreasing Hgb levels during the first and second halves of the titration period, respectively. The data are consistent with initial ARANESP doses that were slightly excessive, effecting an overall increase in Hgb, that, in turn, necessitated reductions in dose.

For subjects assigned to EPO, the dose was largely unchanged between the baseline and evaluation periods. Consistency in the EPO dose across time is expected, considering that subjects were on a stable regimen of EPO at study entry, and in light of the near-zero slope of the Hgb-time relation for EPO (Figure 5). The mean weight-adjusted EPO dose during the evaluation period was 177 U/kg/week.

The sponsor performed a comparison of EPO and ARANESP doses during the evaluation period, based on the proportionality of 200 U EPO = 1 μg ARANESP. For these analyses, a finding of no difference would suggest that the proportionality is correct. The analyses suggested, in fact, that there *was* a difference in doses between groups; however, the sponsor discounted this finding, observing that the data were not normally distributed, and noting that non-parametric analyses do not show a difference between treatment groups.

Reviewer's Comments: The sponsor's interpretation, that ARANESP-equivalent doses were similar in the two treatment groups at end-of-study, ignores the apparent disparity between groups and is not compelling. The sponsor's inability to demonstrate a statistically significant difference between groups is not tantamount to proving equivalence. A more appropriate interpretation of the data is that the sponsor underestimated the potency of ARANESP relative to EPO when conceiving this study. Thus, the relation 1 μg ARANESP = 200 U EPO, derived empirically on the strength of limited data, may not have been optimal. CBER performed exploratory analyses (below) in an attempt to find a more accurate dose proportionality between ARANESP and EPO.

Study 200: As previously noted (page 59 and Figure 4), baseline EPO doses were substantially lower in Study 200 than in Study 117, with median doses of 6,000 compared to 12,000 U/week, respectively. Thus, the median starting ARANESP dose was correspondingly less in Study 200 (30 μg/week), compared to 46 μg/week in Study 117. The median evaluation ARANESP dose was unchanged at 30.0 μg/week (0.44 μg/kg/week on a per-weight basis). The lack of change in dose is consistent with the near-zero slope of the Hgb-time relation for ARANESP in this study (Figure 7).

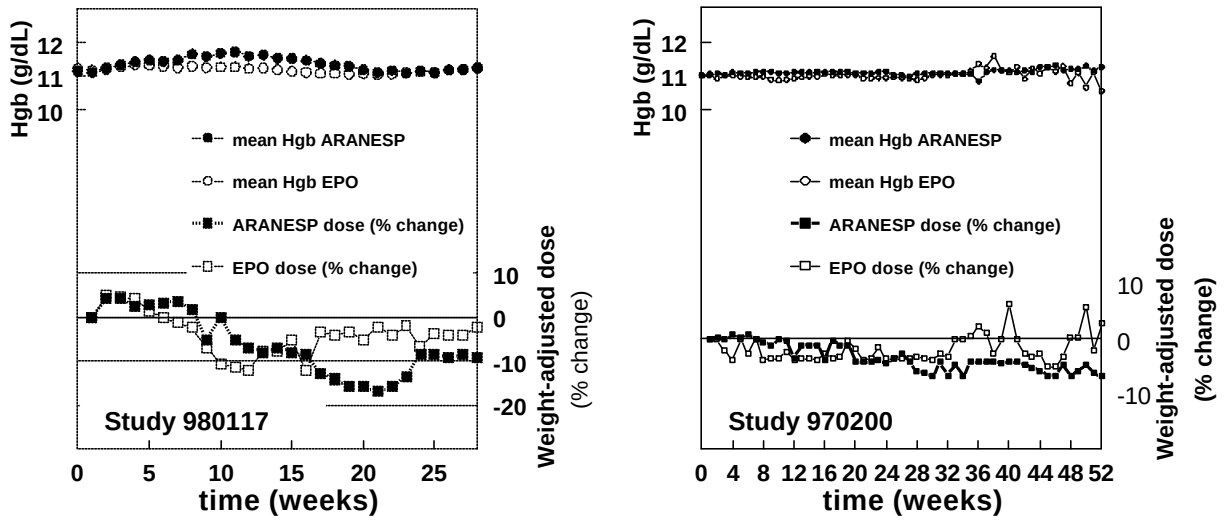
For the EPO group, the weekly EPO dose increased slightly, from a mean of 6,673 U/week during the baseline period to 6,925 U/week during the evaluation period. The mean evaluation period EPO dose was 103 U/kg/week on a per weight basis.

For the evaluation period of this study, the ratio between mean ARANESP dose and mean EPO dose was 202 U EPO/μg ARANESP.

CBER's Analysis of the Relation Between Hgb, Study Agent Doses, and Time

Figure 10 shows the interaction between weekly mean Hgb values (open and filled circles, upper plots) and weekly ARANESP and EPO doses (open and filled squares, lower plots) for Study 117 (left) and Study 200 (right). Time (weeks) is shown continuously, without regard for specific titration or evaluation periods. Doses of study agents were calculated as median weight-adjusted weekly dose, and represented as percent change of starting dose.

Figure 10: Relation Between Median Weight-Adjusted Study Agent Doses and Mean Hgb Concentration by Week – Study 117 (Left) and Study 200 (Right)



For Study 117 (left), the downward shift of the median EPO dose with time suggests that the baseline EPO doses were excessive, and that continuation of EPO at the initial doses would have led to unacceptably high Hgb levels. In Study 200 (right), median EPO doses tended to decrease to a smaller extent. In both studies, ARANESP doses were ultimately titrated downward, approximately -7% to -20 % relative to the EPO doses. This suggests that the original conversion factor (1 μg ARANESP per 200 Units EPO) was, on the whole, excessive. A 7% – 20% increase in the proportionality factor would place it between 214 and 240 Units EPO/μg ARANESP.

Sponsor's Analyses of the Proportionality Between Starting EPO and Final ARANESP Doses:

The sponsor analyzed the EPO → ARANESP conversion factor for all studies in which subjects were converted from EPO to ARANESP (largely Studies 117 and 200). Within-subject estimates of conversion factors were calculated by dividing the baseline weekly EPO dose by the mean weekly ARANESP dose during treatment weeks 21 through 24. Subgroup analyses (demographics, baseline Hgb, baseline EPO dose, dose frequency, route of administration, dialysis modality, and region) indicated that the dose-conversion factor varied with baseline EPO dose and route of administration Table 12. Dose-conversion factors increased with increasing baseline EPO dose, and tended to be higher for IV administration than for SC administration.

Table 12: Estimated IV and SC Dose Conversion – EPO to ARANESP

	Conversion factor for IV dosing		Conversion factor for SC dosing	
	Mean	95% CI	Mean	95% CI
Baseline EPO Dose (U/wk)				
3000	193	(179, 208)	185	(173, 198)
6000	227	(216, 239)	208	(196, 220)
9000	250	(237, 263)	219	(206, 232)
12000	267	(251, 284)	226	(208, 246)
15000	282	(263, 303)	231	(205, 261)
18000	294	(271, 318)	235	(200, 276)
21000	305	(279, 333)	238	(195, 291)
24000	314	(285, 345)	240	(189, 305)
Combined	236	(224, 248)	203	(194, 214)

CBER Exploratory Analysis on Proportionality Between EPO and ARANESP Doses

Whereas the sponsor evaluated the proportionality between baseline EPO dose and ARANESP dose on Weeks 21 – 24, CBER evaluated the relation between *cumulative mean* weekly ARANESP dose (total ARANESP dose received, divided by weeks on study) and baseline EPO dose for all subjects assigned to ARANESP in both studies. These analyses were performed for both weight-adjusted and unadjusted doses. (A single subject in Study 117 was reported to have a baseline EPO dose of 120,000 units, more than twice that of the subject with the second highest baseline dose [54,000 units]. This subject was eliminated from the these analyses.)

For both weight-adjusted and unadjusted analyses, the mean dose proportionality was ~260 units EPO per μg ARANESP for Study 117, and 200 units EPO per μg ARANESP for Study 200. Over both studies, the mean proportionality was 244 units EPO per μg ARANESP.

These analyses show apparent variability in the conversion factors, and underscore the importance of careful monitoring for all subjects. Use of conservative estimates of the conversion factor should help to prevent rapid increases in Hgb, with the attendant risk of cardiovascular events.

Experience With QOW ARANESP Administration:

In Study 200, 95% of the 41 subjects in the pP analysis group who had been receiving QW EPO at baseline were able to be maintained on QOW ARANESP. (Study 117 enrolled only subjects on TIW EPO, and all who were assigned to ARANESP were to receive the agent weekly).

RBC Transfusions:

This was considered an efficacy endpoint in Study 200, only. Though the frequency of RBC transfusions was a safety endpoint in Study 117, the data are presented in this section for consistency.

Study 117: The incidences of RBC transfusions were low and balanced between treatment groups. Throughout the dose titration and evaluation periods, 17 subjects (10%) in the ARANESP group and 38 subjects (11%) in the EPO group underwent ≥1 RBC transfusion.

Study 200: Relative to the North American study, there were substantially more subjects with RBC transfusions in Study 200. Overall, 95 of 519 subjects (18%) received ≥1 RBC transfusion. There numbers were similar between treatment groups, with ≥1 RBC transfusion reported in 19.1% of subjects in the ARANESP group and 16.8% of subjects in the EPO group.

Safety Endpoints:

Exposure to Study Agents:

Study 117: One hundred sixty-nine (169) and 335 subjects received ARANESP and EPO, respectively. The respective mean times on study agent were 26 and 25 weeks. Approximately 85% of subjects received study agents for ≥ 25 weeks in both groups. The weight-corrected mean weekly ARANESP dose was 0.82 μg/kg/week (median 0.64 μg/kg/week).

Study 200: Three hundred forty-six (346) subjects received ARANESP, with a mean exposure of 44 weeks. The weight-corrected mean weekly dose was 0.62 μg/kg/week. One hundred seventy-three (173) subjects received EPO, with a mean exposure time of 46 weeks.

Deaths:

Study 117: There were 9 deaths (5%) in the ARANESP group and 23 (7%) in the EPO group (overall incidence 6%). As is typical of a CRF patient population, cardiovascular events were the leading cause of death, occurring in 3 ARANESP (2%) and 17 EPO (5%) subjects. Investigators reported all deaths as unrelated to study agent. By Cox-regression analysis, the hazard ratio for time to death was 0.76, with 95% CI = 0.35 to 1.65.

Study 200: A total of 52 deaths (12% ARANESP, 6% EPO) occurred within the 28 days after the last dose of study agent or final assessment, whichever was later. The hazard ratio for death was 1.92, with 95% CI = 0.99 to 3.74 (i.e., nearing statistical significance). These deaths included 6 ARANESP subjects who died after entering rollover safety study ARANESP 980160. The largest between-group difference in deaths occurred during the 28 days after the last dose of study drug, or last assessment (4% ARANESP, 1% EPO). Deaths were reported by investigators as unrelated to study agents, and appeared to result from co-morbid conditions.

Deaths for all ARANESP studies are considered together in CBER's integrated analysis of safety.

Serious Adverse Events:

Study 117: The numbers of subjects with at least 1 SAE were similar in the ARANESP and EPO groups (38% and 36%, respectively). Events that occurred at a subject incidence of 3% or greater were thrombosis of vascular access (8% ARANESP, 6% EPO), pneumonia (5% ARANESP, 3% EPO), GI hemorrhage (4% ARANESP, 1% EPO), chest pain (3% ARANESP, 0% EPO), and cardiac failure (2% ARANESP, 3% EPO). Other SAEs had a subject incidence of 2% or less.

Study 200: Fifty-four percent (54%) of ARANESP-treated subjects and 49% of EPO-treated subjects reported at least 1 SAE. The nature and incidence of events were similar for both treatment groups. Thrombosis of vascular access (8% in each group) and dyspnea (4% ARANESP, 3% EPO) were the most common SAEs. Other SAEs occurred at an incidence of 3% or less.

Adverse Events:

AEs reported in ≥10% of subjects in either treatment group of either study, regardless of severity and relationship, as tabulated by the sponsor, are summarized in Table 13. AEs are listed in order of decreasing frequency in ARANESP treatment groups of both studies.

Table 13: Subject Incidence of Adverse Events With a Frequency [3] 10% in Either Group by Descending Order of Incidence

	Study 117		Study 200	
	ARANESP	**EPO**	**ARANESP**	**EPO**
n	169	335	346	173
n (%) of Subjects Reporting AEs	158 (93%)	332 (99%)	333 (96%)	165 (95%)
Hypotension	41 (24%)	61 (18%)	136 (39%)	66 (38%)
Myalgia	36 (21%)	73 (22%)	117 (34%)	62 (36%)
Hypertension	48 (28%)	80 (24%)	103 (30%)	48 (28%)
Diarrhea	36 (21%)	76 (23%)	89 (26%)	41 (24%)
Infection Upper Respiratory	45 (27%)	90 (27%)	70 (20%)	36 (21%)
Nausea	49 (29%)	92 (27%)	62 (18%)	34 (20%)
Chest Pain	35 (21%)	50 (15%)		
Headache	32 (19%)	59 (18%)	74 (21%)	36 (21%)
Vomiting	34 (20%)	70 (21%)	68 (20%)	42 (24%)
Dyspnea	44 (26%)	67 (20%)	51 (15%)	28 (16%)
Pain Abdominal	28 (17%)	56 (17%)	56 (16%)	36 (21%)
Arthralgia	22 (13%)	40 (12%)	61 (18%)	31 (18%)
Pain Limb	30 (18%)	53 (16%)	52 (15%)	32 (18%)
Edema Peripheral	32 (19%)	62 (19%)	49 (14%)	23 (13%)
Fatigue	23 (14%)	45 (13%)	50 (14%)	15 (9%)
Pruritus			47 (14%)	9 (5%)
Dizziness	28 (17%)	57 (17%)	38 (11%)	25 (14%)
Cough	20 (12%)	42 (13%)	46 (13%)	17 (10%)
Thrombosis Vascular Access	27 (16%)	59 (18%)	34 (10%)	15 (9%)
Fever	16 (9%)	39 (12%)	40 (12%)	13 (8%)
Access Complication	18 (11%)	48 (14%)		
Bronchitis			34 (10%)	14 (8%)
Pain Back	15 (9%)	37 (11%)	35 (10%)	27 (16%)
Fluid overload			33 (10%)	15 (9%)
Access hemorrhage			31 (9%)	22 (13%)
Influenza-like symptoms			27 (8%)	21 (12%)
Asthenia	10 (6%)	34 (10%)		

Reviewer's Comments: **CBER found numerous AEs that had been miscoded or incorrectly mapped by the sponsor. Complete analyses of AEs from the ARANESP development**

program as a whole, with corrected classification and mapping, are presented in CBER's integrated analyses of safety.

HTN, MI, TIA, TVA, Convulsions, and Cerebrovascular Disorders:

Particular attention was given to 6 AEs, typically associated with an ESRD population receiving exogenous erythropoietins. These events include HTN, acute MI, TIA, TVA, convulsions and cerebrovascular disorders, and their incidences are shown in Table 14. The overall incidence rates for each of these 6 events were similar between the ARANESP and EPO treatment groups in both studies. Among subjects of African ancestry in Study 117, worsening HTN was reported in 23 of 69 ARANESP-treated subjects of (33%), compared with 23/129 EPO-treated subjects (18%). However, compared to African Americans in the EPO group, ARANESP-treated subjects tended to have a greater proportion of mild to moderate (rather than severe) hypertensive events, and fewer events requiring hospitalization.

Table 14: Subject Incidence of HTN, Cerebrovascular Disorders, Convulsions, MI, TVA and TIA

	Study 117		Study 200	
	ARANESP	**EPO**	**ARANESP**	**EPO**
n (%) of Subjects	169	335	346	173
Hypertension	48 (28%)	80 (24%)	103 (30%)	48 (28%)
Cerebrovascular Disorder	1 (1%)	4 (1%)	6 (2%)	2 (1%)
Convulsions	2 (1%)	6 (2%)	6 (2%)	3 (2%)
Myocardial Infarction	4 (2%)	10 (3%)	5 (2%)	3 (2%)
Thrombosis Vascular Access	27 (16%)	59 (18%)	34 (10%)	15 (9%)
Transient Ischemic Attack	2 (1%)	1 (0%)	1 (0%)	1 (1%)

Withdrawals Due to Adverse Events:

Study 117: There were 23 withdrawals due to AEs; 6 (4%) in the ARANESP group and 17 (5%) in the EPO group; 5 in each group were for SAEs.

Study 200: There were 15 withdrawals due to AEs: 12 (3%) in the ARANESP group and 3 (2%) in the EPO group, with 9 withdrawals (3%) in the ARANESP group and all 3 withdrawals (2%) in the EPO group for SAEs.

Within-Subject Variance of Hgb:

Study 117: Within-subject variance of Hgb was determined for 4 different intervals during the study: weeks 1–12; 13–20; 21–28; and 17–28 (the latter interval at CBER's request). The means and standard deviations of variance were similar between the 2 treatment groups during weeks 1–12 and 13–20, whereas the mean variance of the ARANESP group during weeks 21–28 and 17–28 tended to be greater than that of the EPO group. For weeks 17–28, mean ± SD variance was 0.50 ± 1.35 g^2/dL^2 for the ARANESP group and 0.28 ± 0.58 g^2/dL^2 for the EPO group ($p=0.022$, Wilcoxon rank-sum test).

Reviewer's Comments: The interpretation of mean within-subject variance, within a clinically relevant framework, is not straightforward. The difference between groups does suggest, however, that changes in Hgb with respect to time were more pronounced in ARANESP- versus EPO-treated subjects, during the week 21–28 evaluation period. Multiple additional safety analyses performed by the sponsor and by CBER (see below) suggest that this difference, though statistically significant, is not of major clinical importance.

The sponsor conducted post-hoc analyses in which a single blinded reviewer assessed the Hgb values, and eliminated those that appeared to be "medically implausible." Fifty-four (54) Hgb values were removed in this process, constituting 0.4% of total study values (21 ARANESP; 32 EPO). With elimination of these Hgb values, variance in Hgb was similar between the ARANESP and EPO groups. The sponsor also analyzed the incidences of AEs in subjects with Hgb variance less than or greater than 0.6 g^2/dL^2 (90^{th} percentile), and found no differences within or between treatment groups.

Reviewer's Comments: The study protocol included no prospective rule(s) for elimination of implausible Hgb values, and the post-hoc censoring of data is not acceptable. Elimination of outliers will reduce overall variance, and therefore reduced the magnitude of difference between the variances of the treatment groups. Whereas a fraction of the censored Hgb values were physiologically implausible and likely reflected laboratory or clerical error, CBER found that the majority of the censored values simply defied trends in the data. Such values are not infrequently encountered in clinical practice, particularly in a CRF dialysis population, and there are no grounds for their elimination.

Study 200: Within-subject variance of Hgb was determined for weeks 1–12, 13–24, 25–32, and 21–32. The latter time interval was added to the analysis after CBER requested a similar time interval assessment in Study 117. The difference in within-subject variances of Hgb between treatment groups was most pronounced during weeks 1–12, wherein mean ± SD variance was 0.26±0.53 g^2/dL^2 in the ARANESP group and 0.19±0.29 g^2/dL^2 in the EPO group. During the evaluation period (weeks 25–32), mean within-subject variance in Hgb tended to be lower in the ARANESP group than the EPO group (0.18±0.20 g^2/dL^2 versus 0.23±0.43 g^2/dL^2, respectively).

Reviewer's Comments: Thus, during the dose titration period, there tended to be greater variability in Hgb in the ARANESP versus the EPO group, whereas there was a reversal of this trend during the evaluation period. Given that subjects who were randomized to EPO simply remained on their previous stable EPO dose, the heightened variability in the ARANESP group during the titration period is not unexpected. Moreover, additional safety analyses (below) suggest that this difference was not of major clinical importance.

Maximum Rate of Rise and Decline in Hgb:

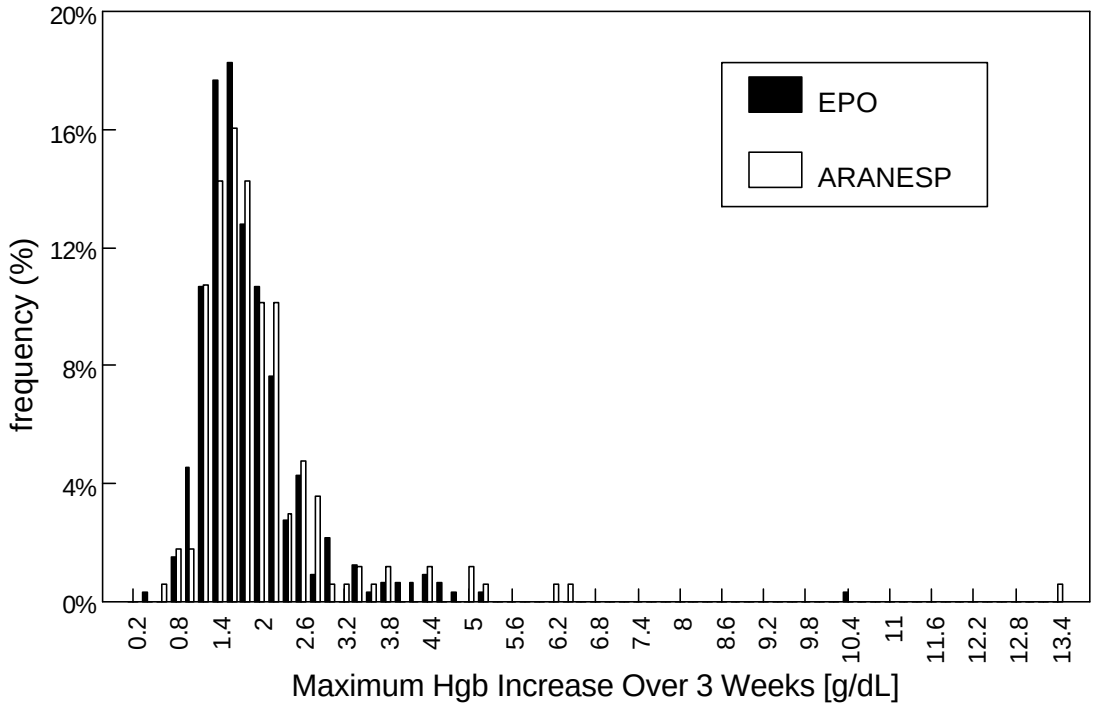
Using linear regression, the maximum rate of increase and decrease in Hgb was calculated for each subject over 3- and 4-week "moving windows" (3 and 4 time points, respectively).

Study 117: The sponsor performed separate analyses for weeks 1–12, weeks 13–20, weeks 21–28, and over the entire study. The median maximum rates of increase and decrease were similar in the two treatment groups. No significant differences were observed between treatment groups

in maximum increase or decrease over 3- or 4-week "windows." The sponsor's summary of the 4-week window data is shown in Table 15.

Reviewer's Comments: The 3-week "moving window" rates of change are more sensitive to variability than the 4-week data. CBER calculated maximum rates of increase over 3-week moving windows, and the distributions are summarized for both treatment groups in Figure 11. A slight rightward shift of the distribution for the ARANESP group is apparent, indicating more rapid increases in Hgb; however, the shift appears to be minimal in magnitude and probably clinically unimportant.

Figure 11: Frequency Distribution: Maximum Rate of Rise in Hgb Over 3 Weeks – Study 980117



Study 200: The sponsor performed separate analyses over the dose titration period (weeks 1–24), the evaluation period (weeks 25–32), and over the entire study. For the 4-week "moving window" analysis within the dose titration period (Table 15), the sponsor reported mean ± SD maximum rates of Hgb increase of 0.45 ± 0.25 and 0.37 ± 0.27 g/dL/week in the ARANESP and EPO groups, respectively, a difference that was statistically significant. During the same period, maximum decreases in Hgb (mean ± SD) were –0.47 ± 0.30 and –0.41 ± 0.23 g/dL/week in the ARANESP and EPO groups, respectively. The differences in maximum rates of Hgb decrease were also considered to be statistically significant.

Table 15: Maximum Rates of Change in Hgb Over 4-Week "Windows:" Studies 117 and 200

	Study 117		Study 200	
	ARANESP	**EPO**	**ARANESP**	**EPO**
Maximum Hgb Increase Over 4 weeks (g/dL)				
Titration Period				
Mean	0.48	0.45	0.45	0.37
Median	0.43	0.40	0.39	0.31
SD	0.25	0.27	0.25	0.27
Quartiles	0.32, 0.57	0.28, 0.55	0.3, 0.5	0.3, 0.4
Range	0.0 to 1.6	0.0 to 2.3	-0.1 to 2.4	-0.3 to 2.0
N	166	324	341	173
Evaluation Period				
Mean	0.31	0.29	0.23	0.26
Median	0.26	0.25	0.21	0.20
SD	0.23	0.22	0.22	0.27
Quartiles	0.15, 0.42	0.14, 0.39	0.1, 0.3	0.1, 0.3
Range	0.0 to 1.5	0.0 to 1.5	-0.7 to 1.6	-0.4 to 1.5
N	131	266	304	156
Maximum Hgb Decrease Over 4 weeks (g/dL)				
Titration Period				
Mean	-0.54	-0.49	-0.47	-0.41
Median	-0.44	-0.44	-0.39	-0.36
SD	0.34	0.26	0.30	0.23
Quartiles	-0.31, -0.71	-0.31, -0.63	-0.6, -0.3	-0.5, -0.3
Range	-0.1 to -2.0	0.0 to -1.8	-3.0 to 0.2	-1.3 to 0.0
N	162	325	341	173
Evaluation Period				
Mean	-0.34	-0.27	-0.23	-0.23
Median	-0.23	-0.22	-0.21	-0.18
SD	-0.42	-0.25	0.25	0.24
Quartiles	-0.14, -0.40	-0.12, -0.36	-0.4, -0.1	-0.3, -0.1
Range	0.0 to -3.6	0.0 to -2.7	-1.5 to 1.0	-1.1 to 0.3
N	123	246	304	156

Reviewer's Comments: For subjects assigned to ARANESP, the starting ARANESP dose was estimated from the baseline EPO dose. In contrast, subjects assigned to EPO were known to have a stable Hgb within the target range on a stable EPO regimen, and the regimen was unchanged. Thus, the difference between groups with respect to variability in the titration period is not unexpected. For Study 200, the presence of negative values in the ranges of maximum Hgb *increases* suggests an error(s) in the sponsor's analyses (i.e., negative values indicates *decreases* in Hgb versus time). CBER recapitulated these analyses (data not shown). Though the ranges do not include negative values, the results are otherwise generally consistent.

Numbers of Subjects with Dose Adjustments:

Study 117: In the dose titration period, similar numbers of subjects required no dose adjustments in the two treatment groups (Table 16), and there were trends in favor of excess dose decreases and fewer dose increases in the ARANESP group. During the evaluation period, however, there tended to a greater percentage of subjects with no dose changes or dose increases in the

ARANESP group. These trends were offset by larger numbers of subjects with both dose increases and decreases in the EPO group.

Table 16: Subjects with Dose Adjustments (³ 20% of Baseline Dose) – Study 117

	ARANESP	EPO
Dose Titration Period		
Number	169	335
No Change [N (%)]	53 (31.4%)	91 (27.2%)
Increase Only [N (%)]	25 (14.8%)	66 (19.7%)
Decrease Only [N (%)]	37 (21.9%)	46 (13.7%)
Both Increase & Decrease [N (%)]	54 (32.0%)	132 (39.4%)
Total Adjusted [N (%)]	116 (68.6%)	244 (72.8%)
Evaluation Period		
Number	149	293
No Change [N (%)]	84 (56.4%)	148 (50.5%)
Increase Only [N (%)]	37 (24.8%)	57 (19.5%)
Decrease Only [N (%)]	15 (10.1%)	34 (11.6%)
Both Increase & Decrease [N (%)]	13 (8.7%)	54 (18.4%)
Total Adjusted [N (%)]	65 (43.6%)	145 (49.5%)

Study 200: The proportions of subjects with dose adjustments were similar in both treatment groups throughout the study. During the dose titration period, the proportions of subjects with dose adjustments were 51.7% and 46.8% in the ARANESP and EPO groups, respectively (data not shown). During the evaluation period, the respective percentages were 28.3% and 30.6%.

Laboratory Abnormalities:

Study 117: Mean changes from baseline to end-of-study were comparable between treatment groups for laboratory biochemistry values, electrolytes, leukocytes, and platelets. There were statistically significant differences between groups with respect to change from baseline to end-of-study for blood urea nitrogen (BUN), creatinine, uric acid and sodium; however, the absolute differences were small.

Study 200: Changes in laboratory values, including biochemistry values, electrolytes, leukocytes, platelets, and coagulation tests, were comparable between treatment groups.

Iron Indices and Iron Supplementation:

Study 117: Median serum ferritin and transferrin saturation were virtually identical in the two treatment groups at baseline. Median changes for serum ferritin and transferrin saturation from baseline to end-of-study were -3.7 ng/mL and –4.0% for the ARANESP group, and 26 ng/mL and –4.8% for the EPO group. The subject incidence of iron deficiency was similar in the two groups throughout the study. Iron supplementation was similar for both treatment groups, administered to 78% and 79% of subjects by the IV route, and administered orally to 31% and 36% of subjects in the ARANESP and EPO groups, respectively. The mean respective weekly IV iron doses were 136 mg and 148 mg. The average weekly doses of oral iron were 820 mg and 895 mg, respectively.

Study 200: Median baseline ferritin was 317 µg/L for the ARANESP group, versus 284 µg/L for the EPO group. Mean changes in ferritin through end-of-study were –9.0 ng/mL versus 7.3 ng/mL for the ARANESP and EPO groups, respectively. Ninety-nine percent (99%) of the subjects at baseline and 95% at the end of the study had serum ferritin >100 ng/mL, indicating that most subjects were iron replete based on standard measures. The subject incidence of iron deficiency was similar in both groups throughout the study. Eighty-seven percent (87%) of subjects received 1 or more IV iron injections in both treatment groups, at a median dose of 100 mg/week during the titration, evaluation, and maintenance periods for both groups.

ARANESP and EPO Antibodies:

Study 117: Baseline and follow-up antibody assay results were obtained in 163 of 196 ARANESP subjects, and 321 of 335 EPO subjects. All subjects were seronegative at baseline. Final antibody assays were obtained >28 weeks after the initial dose in ~85% of subjects in both groups (median follow-up was 29 weeks in both groups). All assays were negative. In total, 158 ARANESP-treated subjects had antibody assays ≥10 weeks after their initial dose, and all assays were negative.

Study 200: Antibody assay results were available for 343 of 346 subjects in the ARANESP group, and all 173 subjects in the EPO group. All subjects were seronegative at baseline. Final assays were obtained >32 weeks after the initial dose in 86% of ARANESP-treated subjects and 89% of EPO-treated subjects. All assays were negative. In all, 329 ARANESP-treated subjects had anti-NESP antibody assays performed >16 weeks after their initial dose, and all results were negative.

Reviewer's Comment: For both studies together, therefore, 487 ARANESP-treated subjects had antibody assays performed ≥ 10 weeks after initiation of ARANESP treatment, and all assay results were negative.

Vital Signs:

Study 117: There was considerable variation in blood pressure within individual subjects, and no apparent inter-group or subgroup (Caucasian, Black and “other”) differences in systolic and/or diastolic blood pressure shifts. Heart rate was not systematically recorded in this study, and the results are not informative.

Study 200: As in the North American study, there was considerable intra-subject variation in blood pressure, but no apparent inter-group or subgroup differences in heart rate or blood pressure shifts in either direction.

Anti-Hypertensive Medications:

Study 117: The numbers of subjects taking ≥1 antihypertensive medication were similar for the ARANESP and EPO groups (76% and 78%, respectively). The use of antihypertensive medications was comparable between treatment groups by study period and medication class. Changes in anti-hypertensive medication use from baseline to end-of-study were also similar for both groups.

Study 200: The numbers of subjects taking ≥ 1 antihypertensive medication were similar for the ARANESP and EPO groups (64% and 68%, respectively). Antihypertensive medication use was

similar between treatment groups. Changes in antihypertensive agents from baseline to end-of-study were also similar between groups.

Financial Disclosure:

Two investigators and 3 sub-investigators in Study 117 reported ownership of shares of Amgen stock. These financial interests in a small minority of investigators in a study with objective endpoint measures are deemed highly unlikely to importantly affect study conduct or results.

Discussion and Analysis – Studies 117 and 200:

Study 117 and Study 200 were phase 3 active-control studies to assess the safety and efficacy of ARANESP in *maintaining* Hgb concentrations in clinically stable dialysis patients who had been previously maintained on EPO therapy.

Proof of Efficacy:

These studies provide an important safety experience for ARANESP, but do not constitute a rigorous test of the efficacy of the product for the treatment of anemia associated with CRF. In essence, the primary efficacy endpoint of these studies (change in Hgb) is a pharmacodynamic measure. (Hemoglobin is a laboratory parameter that is both readily ascertainable and proximally related to the putative mechanism of action of the study agent [i.e., enhanced erythropoiesis]). Moreover, the investigations were designed such that study agents were titrated to achieve the desired effect. Thus, assuming that ARANESP has erythropoietic activity, the attainment of the primary efficacy endpoint, per se, is practically expected. Aside from the achievement of a target Hgb level, other salient issues include predictability and controllability of the Hgb response, which are tied inextricably to safety.

Subjects in Studies 117 and 200 were not anemic at study entry, given that erythropoiesis had been compensated through the prior use of other recombinant erythropoietins. In reality, the studies assessed the effectiveness of ARANESP in *maintaining* erythropoiesis in previously treated subjects. Moreover, the study entrance criteria selected patients who were likely to respond to ARANESP in a predictable way: 1) The studies were performed in *stable* patients, who could qualify for enrollment only if they had demonstrated relatively constant Hgb concentrations in response to a consistent dose of EPO; 2) The baseline EPO dose provided a means for estimating the starting ARANESP dose. For future patients in whom ASANESP would represent the initial erythropoietic therapy, such information would not be available.

A critical consideration in non-inferiority studies is the ability to provide evidence that the active comparator agent is having a beneficial effect in the subject population studied. Study 117 was planned in collaboration with CBER, and the protocol required documentation of a 1 g/dL increase in Hgb in response to initiation of EPO therapy. Study 200 was conducted in advance of discussions with CBER, and for this study, this condition was not met. Thus, for Study 200, there is some uncertainty as to whether the active comparator was efficacious in the population studied, which to some extent undermines the evidence of ARANESP's efficacy in that study.

Adequate Representation of Special Patient Populations:

Study 200 was randomized in a 2:1 ratio (ARANESP to EPO), whereas Study 117 was inadvertently randomized in a reverse ratio (1:2). Because of this error, the ARANESP subject population in the North American Study 117 was only half of its planned size, importantly affecting

the overall demographic makeup of the studies. Thus, of the 516 subjects randomized to ARANESP across both studies, only 80 (15.5%) were of African descent. Given that nearly half of the U.S. target patient population is of African descent, the under-representation of this patient population in the phase 3 studies represents a significant concern.

Few PD subjects were enrolled in Study 200, and none were enrolled in Study 117 (the latter, by design). Specifically, over both studies, only 4% of subjects were receiving PD. Thus, the PD patient population was also under-represented in the phase 3 program.

Conversion Factor for Substitution of ARANESP for EPO:

For subjects assigned to ARANESP treatment, the initial weekly ARANESP dose was calculated from the baseline weekly EPO dose, using the proportionality 200 Units EPO per μg ARANESP. On the whole, ARARNESP doses required reductions in the range of 10 to 20%, suggesting that the potency of ARANESP was underestimated; however, the data suggest that the relation between baseline EPO dose and ARANESP dose is non-linear, such that a single conversion factor may not be generalizable to all patient populations. Subgroup analyses based on demographic factors, baseline Hgb, baseline EPO dose, dosing frequency, route of administration, and dialysis modality suggested important interactions with route of administration, and in particular, baseline EPO dose. Whereas the conversion factor was ~200 Units EPO per μg ARANESP for subjects who had received lower EPO doses (~3000 Units/week), the conversion factor increased to ~300 Units EPO/μg ARANESP for patients who had been receiving ~18,000 units of EPO weekly. Moreover, the potency of ARANESP tended to be higher when administered by the IV route rather than the SC route, relative to the potency of EPO. The sponsor summarized the data in a table (Table 12), which, in some simplified form, would be of value for use in labeling.

Variability in Hemoglobin Response:

More than one-third of subjects in Study 117 and more than one-fourth of subjects in Study 200 exhibited unstable Hgb concentrations during the evaluation period. This instability was observed despite prolonged periods for dose-titration and stabilization in both studies. There was no apparent disparity in the rates of instability between ARANESP- and EPO-treated subjects in either study.

For Study 117, analyses of within-subject variance of Hgb demonstrated significantly greater variance within the ARANESP group during weeks 17–28. There were no statistically significant differences within other time intervals, or throughout Study 200. The sponsor conducted a post-hoc analysis in which a single blinded reviewer eliminated Hgb values considered to be “medically implausible.” This analysis removed not only medically implausible Hgb values (likely a result of laboratory or clerical errors), but also values that were not consistent with prevailing trends. For such analyses, a positive result is an inability to demonstrate a difference in variance between groups. Given that any intervention designed to remove outliers will reduce variance, the post hoc removal of any outliers is inappropriate for this analysis, and the results are not acceptable for labeling or promotion.

Safety:

Adverse events and laboratory abnormalities appeared typical for the patient population; however, the studies were not powered to detect disparities in the frequencies of events that are relatively serious, yet fairly common in a typical CRF population. Moreover, initiation of erythropoietic therapies in anemic subjects may be associated with risks related to the increased hemodynamic

burden imposed by an expanding extravascular volume, as well as theoretical risks related to increasing blood viscosity (i.e., HTN, thrombotic events, seizures, etc.). By design, these studies did not address the safety of ARANESP in this context.

For additional analysis of safety, see CBER's integrated review of safety.

Uncontrolled, Long-Term, Phase 3 Safety Studies:

Studies 980140 and 980160 are *ongoing, uncontrolled* phase 3 safety studies which will be referred to as Studies "140" and "160," respectively:

- Study 140 is a 52-week study wherein subjects previously receiving EPO are to be switched to ARANESP, with selection of the starting ARANESP dose on the basis of the previous stable EPO dose and an ARANESP:EPO dose proportionality factor.

- Study 160 is a 104-week extension study, in which subjects who completed 52 weeks of ARANESP treatment are to continue on ARANESP for an additional 2 years.

Although these studies are similar with respect to their prolonged periods of treatment and general design, they merit separate review in light of the key difference between them (conversion to ARANESP, involving dose-titration, in Study 140; versus continuance on a stable dose of ARANESP in Study 160).

Study 140 enrolled subjects who had not been included in previous ARANESP studies and who were receiving EPO at baseline. This study enrolled rapidly, completing enrollment between 8/98 and 3/99. In contrast, Study 980160 is enrolling only subjects who have completed other ARANESP studies. Thus, the rapidity of enrollment is inherently limited.

The review of Study ARANESP 140 merits special emphasis because nearly half of all ARANESP-treated subjects in this license application are included in this study.

Study 140 – Phase 3 Safety Study – Conversion of EPO to ARANESP:

Title:	A Study to Assess the Safety of ARANESP Therapy in Patients With End-Stage Renal Disease (ESRD)
Study Period:	August 1998 – ongoing; Subject enrollment completed March 1999; cutoff for interim analysis 6/30/99
Centers:	Fifty-eight (58) centers in Europe and Australia.
Subjects:	709 enrolled
Notes:	This study was not conducted under IND.

Objectives:

To evaluate the safety and tolerability of chronic (≤ 52 weeks) ARANESP therapy and to assess the dose range of ARANESP required to maintain a target Hgb.

Reviewer's Comment: The major objective of the study is to gain adequate experience with the product to comply with the March 1995 ICH-E1A Guideline for Industry ("The Extent of Population Exposure to Assess Clinical Safety").

Design:

This is an ongoing, multicenter, uncontrolled, safety study. Enrollment is complete. Subjects with ESRD receiving either PD or HD, with Hgb maintained on EPO, were to be switched to ARANESP using a standard dose proportionality (200 U EPO → 1.0 µg ARANESP). The route of administration (IV or SC) was to be maintained. For subjects previously receiving EPO on a BIW or TIW schedule, the frequency of ARANESP administration was to be reduced to QW. For subjects receiving EPO on a QW schedule, the frequency of ARANESP administration was to be reduced to once every 2 weeks. The dose of ARANESP is to be adjusted to achieve a target Hgb concentration of 9.0 - 13.0 g/dL and within -1.0 g/dL to +1.5 g/dL of the subject's mean baseline Hgb concentration. ARANESP is to be administered for 52 weeks. Safety is to be assessed by the nature and frequency of AEs, changes in vital signs and laboratory variables, and ARANESP antibody status. Laboratory variables (i.e., hematology, biochemistry, and iron status) are to be assessed at local laboratories. ARANESP antibody assays are to be performed at Amgen. All subjects are to be followed for a period of 4 weeks after the final dose of ARANESP.

Concomitant medications, vitamins, minerals, and other treatments are to be permitted as clinically indicated, with information on concomitant anti-hypertensive medications and IV iron to be recorded in the CRFs. Blood transfusions were not allowed during the screening or baseline periods, but are permissible during the study. Prohibited medications included EPO, androgens, and investigational drugs.

Withdraw is allowed for significant protocol violation(s) or noncompliance, pregnancy, refusal to continue treatment/observations, unacceptable or dose-limiting toxicity, renal transplant, unrelated medical illness or complication, and decisions that discontinuation is in the best interest of the subject? Temporary interruption of ARANESP for Hgb >14 g/dL is planned, but is not meant to trigger subject withdrawal.

Dose Adjustments:

Dose adjustments are to be instituted to maintain Hgb within the target range (-1 to +1.5 g/dL of baseline, and between 9–13 g/dL), as per Study 117 (page 47).

Screening and Baseline Periods; Monitoring:

The baseline Hgb and other laboratory data were to be calculated as the mean of the values obtained during the screening and baseline periods. Hgb concentration is to be assessed weekly during weeks 1–12 and monthly during weeks 13–52. After Week 12, Hgb values out of the target range were to trigger dose adjustments and weekly Hgb assessment for 4 weeks. Biochemical analyses were to be performed every 12 weeks.

Adverse event rates were characterized by subject incidence and event occurrence. Six AEs were prospectively defined because of their clinical significance and potential to be associated with Hgb concentration: HTN, TVA, convulsions, cerebrovascular disorder, MI, and TIA.

ARANESP antibodies were to be assayed before the first dose of ARANESP and at 12-week intervals throughout the study. Two assays were designed to detect anti-NESP antibodies: a radioimmunoprecipitation (RIP) screening assay to detect immunoreactivity to ARANESP and a cell-based bioassay to detect neutralizing antibodies.

Pharmacokinetic Sub-Study 980194:

A subset of 16 subjects scheduled to receive ARANESP SC once weekly were concurrently enrolled in ARANESP Study 980194, a pharmacokinetic study. Subjects underwent two 7-day pharmacokinetic assessments, the first on week 1 and the second on week 8 in which blood samples for NESP serum concentration analyses were drawn before (0) and at 6, 24, 32, 40, 48, 56, 72, 96, 120, and 168 hours after SC ARANESP administration. The second profile was compared with that of the first, to determine if the pharmacokinetics of SC ARANESP changed over time.

Study Population:

Inclusion Criteria:

- Adult subjects with ESRD, receiving HD or PD for ≥ 3 months
- receiving EPO therapy 1, 2, or 3 times weekly, by SC or IV administration, for ≥ 3 months
- mean Hgb 9.5–12.5 g/dL
- adequate iron stores (ferritin ≥ 100 ng/mL or transferrin saturation ≥ 20%) at screening

Exclusion Criteria:

- uncontrolled HTN, grand mal epilepsy within 6 months, congestive heart failure (New York Heart Association (NYHA) Functional Classification class III or IV)
- severe hyperparathyroidism (serum PTH >1000 pg/mL within 12 months [exception: subjects with subsequent parathyroidectomy])
- clinical evidence of infection or inflammatory disease, active peritonitis, active liver disease, ALT or AST > 2X upper limit of normal, chronic hepatitis B infection
- human immunodeficiency virus (HIV), current malignancy (exception: basal cell or squamous cell carcinoma of the skin)
- systemic hematological disease (e.g., sickle cell anemia, hemolytic anemia, myelodysplastic syndromes, hematological malignancy, myeloma)
- major surgery within 3 months (exception: vascular access surgery)
- active bleeding; blood transfusions within 3 months before enrollment or during the screening/baseline period
- androgen therapy within 3 months
- pregnancy or breast feeding; women of child-bearing age were required to be using adequate contraception
- anticipated or scheduled living–related renal transplant

Statistical Plan:

The analyses focused on the nature and incidence of AEs and on the dose range of ARANESP required to maintain the target Hgb concentration. No formal hypothesis testing is planned. The sample size was based on the requirement to comply with the March 1995 ICH-E1A Guideline for Industry (“The Extent of Population Exposure to Assess Clinical Safety”).

Primary Endpoint:

The primary endpoint is the incidence of AEs, to be assessed using the safety analysis set (all subjects who received ≥ 1 dose of ARANESP). The statistical analysis plan introduced the definition of 2 study periods: the titration period (weeks 1–24) and the maintenance period (weeks 25–52). Adverse events and other endpoints were to be summarized for these study periods

separately, as well as for the study overall. (Analyses by period included all subjects who received ≥ 1 dose of ARANESP during that period.) Adverse events were evaluated using 2 methods: 1) subject Incidence – the number and proportion of subjects experiencing a specific AE at any time; and 2) event occurrence – an exposure-adjusted expression defined as total occurrences of an AE across all subjects divided by the total number of subject-months on treatment (a subject-month was defined as 4 weeks). For subjects with multiple reports of the same term, the event was counted only once, using the most severe occurrence of an AE for each subject. Worsening of a pre-existing condition was defined as an event, counted on the date deterioration occurred. Particular attention was given to 6 prospectively-defined AEs, typically associated with an ESRD population receiving exogenous erythropoietins: HTN, MI, TIA, TVA, convulsions, and cerebrovascular disorder.

Secondary Endpoints:

Secondary endpoints included tabulations of total and mean weekly ARANESP dose, maximum frequency of ARANESP administration, and number and proportion of subjects with dose adjustments. Laboratory variables (hematology, chemistry, and iron levels) and vital signs, as well as the incidences of RBC transfusions and antibody formation to ARANESP were all secondary endpoints. Efficacy analyses, to be performed on the safety analysis set, included change in Hgb from baseline and mean Hgb concentration by study week. Within-subject variance of Hgb was to be calculated for the titration and maintenance periods, and for the study overall.

Subgroup Analyses:

Prospectively-defined subgroups for analyses of AEs, dose and frequency of ARANESP administration, and Hgb concentration are:

- frequency of EPO administration at entry into the study (1, 2, or 3 times weekly)
- route of EPO administration at entry into the study (IV or SC)
- dose of EPO administration at entry into the study (in quintiles)
- dialysis modality (HD or PD)
- baseline Hgb concentration
- age group (< 65, ≥ 65, and ≥ 75 years)

Interim Analysis:

A prospectively-planned interim analysis was performed for BLA-filing when data through 6/30/99 were available.

Changes in Protocol and Statistical Methods:

No protocol amendments were implemented during through the interim analysis, and there were no changes to study conduct.

The statistical analysis plan introduced a new definition of the end-of-study for subjects continuing ARANESP therapy beyond 52 weeks by participating in Study 160 (the day before the initial dose of ARANESP in Study 160). As the results presented herein are from interim analyses, none of the subjects have reached end-of-study, and none have yet enrolled in Study 160.

Results:

Enrollment and Disposition of Subjects:

Enrollment began in June 1998 and was completed in March 1999. Seven hundred-nine (709) subjects from 58 centers are participating in the study. The study centers are located in 14 European countries and Australia. Of the 709 subjects enrolled, 6 were withdrawn before the first dose of ARANESP. Therefore, 703 subjects received ARANESP and were included in the sponsor's interim safety and efficacy analyses on data collected through the 6/30/99 cut-off date. At that time, 249 subjects (35%) had completed the titration period and no subject had completed the maintenance period. Safety and efficacy data were available to a maximum of study week 36. The median exposure time was 24.4 weeks (quartiles: 23, 25 weeks). Subject disposition and reasons for discontinuation are summarized in Table 17. The most common reasons for discontinuation were kidney transplant (5.2%), death (2.7%) and withdrawal requested (1.8%).

Protocol Deviations and Treatment Compliance:

Deviations from the study protocol that had the potential to affect the study endpoints were infrequent and relatively unimportant, and are unlikely to have affected the interpretation of the study results. Two subjects received 4 doses of ARANESP from vials that had expired by up to 8 weeks. Five subjects received doses of EPO during the study (1, 1, 2, 4 and 5 doses). The subjects who received 4 and 5 doses were withdrawn from the study at the time they received EPO. Six subjects had no baseline antibody sample.

Table 17: Subject Disposition and Reasons for Discontinuation – Study 140

Total Subjects Enrolled	**709**		
Did Not Receive ARANESP Study Agent	**6 (0.8%)**		
Withdrawal Requested		1 (0.1%)	
Unrelated Medical Condition		1 (0.1%)	
Death on Study		1 (0.1%)	
Kidney Transplant		2 (0.3%)	
Other		1 (0.1%)	
Received ARANESP Study Agent	**703 (99%)**		
Titration Period (Weeks 1 - 24)			
Started		703 (99%)	
Ongoing		361 (51%)	
Completed		249 (35%)	
Discontinued		93 (13%)	
Intolerable Adverse Event			8 (1.1%)
Withdrawal Requested			13 (1.8%)
Unrelated Medical Condition			2 (0.3%)
Adminstrative/Investigator Decision			7 (1.0%)
Lost to Follow-up			3 (0.4%)
Death on Study			19 (2.7%)
Kidney Transplant			37 (5.2'%)
Other			4 (0.6%)
Maintenance Period (Weeks 25 - 52)			
Started	**249 (35%)**		
Ongoing	**216 (30%)**		
Completed	**0 (0%)**		
Discontinued	**33 (5%)**		
Withdrawal Requested		6 (0.8%)	
Unrelated Medical Condition		1 (0.1%)	
Adminstrative/Investigator Decision		2 (0.3%)	
Death on Study		13 (1.8%)	
Kidney Transplant		11 (1.6%)	
Total Ongoing	**577 (81%)**		
Total Discontinued	**132 (19%)**		
Total Completed	**0 (0%)**		

Demographic and Other Baseline Characteristics:

Subject demographics and baseline characteristics for the 703 subjects who received ARANESP are presented in Table 18. Fifty-eight percent (58%) of subjects were male and 94% subjects were Caucasian. The median subject age was 63 years and median weight was 67 kg. Ninety-five percent (95%) of subjects were receiving HD, and the mean baseline Hgb was 11.1 g/dL. Median weekly baseline EPO dose was 6511 units, with 61% of subjects receiving the agent by the SC route; 39% by the IV route.

Table 18: Demographics, Baseline Characteristics and EPO Administration – Study 140

Number of Subjects: 703

Gender [n, (%)]	
Female	292 (42%)
Male	411 (58%)
Race [n, (%)]	
Caucasian	661 (94%)
Black	20 (3%)
Asian	5 (1%)
Other	17 (2%)
Age (years)	
Mean	60
Median (quartiles)	63 (50, 72)
Range	18 - 91
Weight (kg)	
Mean	68.3
Median (quartiles)	67.2 (58.5, 76.0)
Range	37 - 121
Cause of Renal Failure [n, (%)]	
Glomerulonephritis	174 (25%)
Hypertension	94 (13%)
Diabetes	87 (12%)
Other urologic	54 (8%)
Polycystic kidney disease	47 (7%)
Other	164 (23%)
Unknown, unconfirmed	73 (10%)

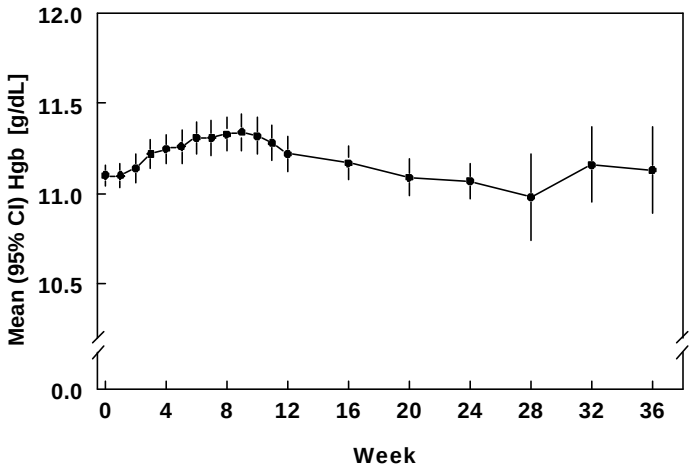
Mode of dialysis [n, (%)]	
Hemodialysis	666 (95%)
Peritoneal	37 (5%)
Baseline Hb (g/dL)	
Mean	11.1
Median (quartiles)	11.1 (10.5, 11.7)
Range	9.5 - 12.5
EPO dose at study entry (U/wk)	
Mean	6511
Median (quartiles)	6000 (4000, 9000)
Range	1000 - 30000
Freq of EPO administration at study entry [n, (%)]	
1 X per week	157 (22%)
2 X per week	203 (29%)
3 X per week	343 (49%)
Route of EPO administration at study entry [n, (%)]	
Subcutaneous	429 (61%)
Intravenous	274 (39%)

Efficacy:

Hemoglobin was controlled within the target range of 9–13 g/dL and the mean Hgb was maintained at a stable level relative to the baseline for up to 36 weeks, though data are sparse after week 24 (Figure 12). The mean (95% CI) baseline Hgb was 11.1 g/dL (11.1, 11.2). The mean change in Hgb from baseline was 0.12 g/dL (0.02, 0.22) at week 12, -0.03 g/dL (-0.12, 0.06) at week 24, and -0.08 g/dL (-0.29, 0.12) at week 36.

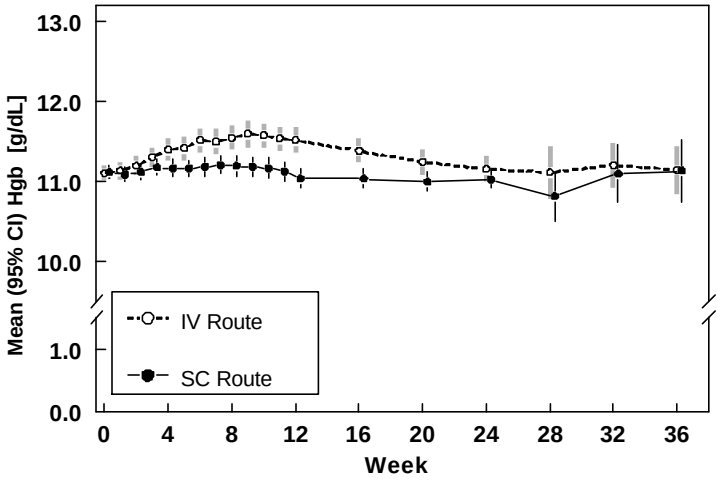
There appeared to be a slight disparity in response between subgroups using the IV and SC routes of administration, though the

Figure 12: Mean (95% CI) Hgb by Study Week – Study 140



means of both groups remained well within the target range (Table 18). After week 5, Hgb tended to increase to a greater extent in the subgroup receiving ARANESP by the IV route, relative to the SC subgroup. The peak difference (0.48 g/dL) occurred at week 12. By week 24, the mean Hgb in the 2 groups converged. Data obtained after week 24 are too sparse to be meaningful.

Figure 13: Mean (95% CI) Hgb by Route of EPO Administration at Study Entry – Study 140



Reviewer's Comments: Though subjects who received IV ARANESP appeared to reach higher mean Hgb values than subjects who received SC ARANESP, little can be inferred regarding a difference in potency/ bioavailability between SC and IV ARANESP. This is because baseline EPO dosing requirements may differ by route of administration. Specifically, with respect to EPO, it has been shown that the mean dose required to maintain hematocrit in the 30–33% range is roughly one-third lower with SC administration than with IV administration.[1] For the present study, subjects were converted from EPO to NESP while maintaining the route of administration (SC or IV), and using the same dosing conversion factor for each route. Thus, comparison of SC and IV ARANESP dosing requirements in the present study is confounded by a potential disparity in EPO dosing requirements, used to calculate the initial ARANESP dose.

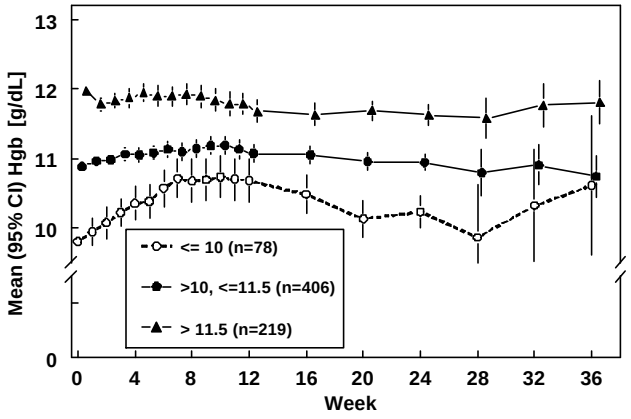
The sponsor also analyzed the Hgb versus time relation by baseline Hgb, baseline EPO dose, baseline frequency of EPO administration, and dialysis modality.

Subjects were divided into 3 subgroups on the basis of baseline Hgb: Hgb ≤ 10 g/dL; Hgb >10 and ≤11.5 g/dL; and Hgb >11.5 g/dL (Figure 14). The 2 subgroups with the higher mean baseline Hgb values maintained relatively flat (near-zero slope) Hgb versus time relations throughout the study, whereas there was an increase in mean Hgb in subjects with baseline Hgb ≤10 g/dL. This occurred primarily during the initial 7 weeks of the study (from the mean increasing from 9.8 g/dL to 10.7 g/dL). Thus, subjects enrolled in the lower range of allowable Hgb concentrations appeared to respond to ARANESP, as administered in the study. (Note, N's in Figure 14 refer to numbers at baseline; data are sparse after Week 24.)

[1] Kaufman JS, et al. *New Engl J Med* 1998; 339:578

A similar analysis was performed for 5 subgroups based on baseline EPO dose (data not shown). For the lowest pre-study EPO dose subgroup (EPO dose < 3000 U/week), the Hgb versus time relation was relatively flat throughout the study, whereas there appeared to be periods of increasing Hgb during the initial 7 weeks on study for the 4 subgroups with higher pre-study EPO doses (EPO dose > 3000 U/week). Moreover, the rates of rise in the subgroups appeared to be dose-related. Hgb values were similar for subgroups based on baseline frequency of EPO administration and dialysis modality.

Figure 14: Hemoglobin Versus Time Relation, as a Function of Baseline Hemoglobin



Hemoglobin Relative to Target Range:

The proportion of subjects within the Hgb target range of 9 – 13 g/dL and within -1.0 to +1.5 g/dL of baseline Hgb decreased through the first 7 weeks of the study, leveling off at ~70%, thereafter

Table 19: Numbers of Subjects Within Target Range – Study 140

	N (%) Within Target Range (Hgb 9 -13 g/dL), and Within -1.0 to +1.5 g/dL of Baseline Hgb			N (%) Within Target Range (Hgb 9 - 13 g/dL)		
	Above	Within	Below	Above	Within	Below
Week 1	17 (2.5%)	627 (90.9%)	46 (6.7%)	7 (1.0%)	671 (97.2%)	12 (1.7%)
Week 2	39 (5.6%)	590 (85.4%)	62 (9.0%)	24 (3.5%)	655 (94.8%)	12 (1.7%)
Week 3	49 (7.1%)	570 (82.6%)	71 (10.3%)	27 (3.9%)	652 (94.5%)	11 (1.6%)
Week 4	70 (10.2%)	542 (78.8%)	76 (11.0%)	36 (5.2%)	637 (92.6%)	15 (2.2%)
Week 5	86 (12.7%)	512 (75.4%)	81 (11.9%)	47 (6.9%)	614 (90.4%)	18 (2.7%)
Week 6	99 (14.6%)	486 (71.7%)	93 (13.7%)	54 (8.0%)	608 (89.7%)	16 (2.4%)
Week 7	113 (16.7%)	458 (67.9%)	104 (15.4%)	62 (9.2%)	599 (88.7%)	14 (2.1%)
Week 8	113 (16.8%)	463 (68.8%)	97 (14.4%)	64 (9.5%)	583 (86.6%)	26 (3.9%)
Week 9	116 (17.3%)	462 (69.0%)	92 (13.7%)	64 (9.6%)	579 (86.4%)	27 (4.0%)
Week 10	116 (17.5%)	443 (66.9%)	103 (15.6%)	59 (8.9%)	577 (87.2%)	26 (3.9%)
Week 11	106 (16.0%)	456 (68.9%)	100 (15.1%)	51 (7.7%)	578 (87.3%)	33 (5.0%)
Week 12	96 (14.9%)	437 (68.0%)	110 (17.1%)	44 (6.8%)	571 (88.8%)	28 (4.4%)
Week 16	82 (12.6%)	456 (70.2%)	112 (17.2%)	33 (5.1%)	588 (90.5%)	29 (4.5%)
Week 20	68 (10.7%)	456 (71.9%)	110 (17.4%)	31 (4.9%)	569 (89.7%)	34 (5.4%)
Week 24	60 (9.6%)	455 (72.7%)	111 (17.7%)	35 (5.6%)	568 (90.7%)	23 (3.7%)

(Table 19, left). The percentage of subjects within target range, but not necessarily within –1 g/dL to +1.5 g/dL of baseline Hgb, decreased through the initial 9 weeks, and remained in the 87–91% range after Week 9 (Table 19, right). Generally, the proportions of subjects with Hgb concentrations exceeding the range were in excess of those below the range.

Reviewer's Comments: Subjects who exceed the Hgb target range may be exposed to increased risk of AEs. The sponsor's data, summarized in Table 19, are tabulated by week, rather than by subject, and underestimate the individual subject risk of exceeding the upper limit of the Hgb target range. CBER assessed the proportions of subjects who exceeded various Hgb cut-points (Table 20). At some point during the (mean) 24-week duration of the study, 27.6% of subjects exceeded the 13 g/dL upper limit of the Hgb target range, and 10.1% exceeded the limit by > 1 g/dL. Approximately 4% of subjects exceeded the limit by 1.5 g/dL at some point during the study. The large proportion of subjects exceeding the target range is concerning, particularly in light of the fact that these subjects had been maintained on EPO prior to study entry, and the baseline EPO dose provided a means to estimate the initial ARANESP dose requirements. For an EPO-naïve patient population, a population that is actually anemic at baseline and for whom selection of an initial ARANESP dose can not be based on prior experience with another erythropoietin, the percentage of patients exceeding the target range could be substantially higher. This concern is further magnified because subjects in this study were carefully monitored with protocol-driven ARANESP dose adjustments. Presumably, in clinical practice, monitoring would be less intensive, and titration would be less vigilant, with both factors serving to increase the proportion of patients who exceed the target range, and to increase the magnitude by which the target is exceeded. The ramifications of exceeding the target range are discussed in CBER's integrated analyses of safety.

Table 20: Proportions of Subjects With Hgb Values Exceeding Cut Points (Study 140)

Total N = 703

		number	percent
Hgb above	**12.0 g/dL**	437	62.2%
Hgb above	**12.5 g/dL**	294	41.8%
Hgb above	**13.0 g/dL**	194	27.6%
Hgb above	**13.5 g/dL**	118	16.8%
Hgb above	**14.0 g/dL**	71	10.1%
Hgb above	**14.5 g/dL**	27	3.8%
Hgb above	**15.0 g/dL**	6	0.9%

Table 21: Dose Adjustments – Study 140

Number of Subjects = 703

Dose Withheld	
None	646 (92%)
1	52 (7%)
2	5 (1%)
Dose Restarted	
1	37 (5%)
2	4 (1%)
Dose Decreases	
None	505 (72%)
1	69 (10%)
2	65 (9%)
3	56 (8%)
4	5 (1%)
5	2 (0%)
6	1 (0%)
Dose Increases	
None	431 (61%)
1	112 (16%)
2	55 (8%)
3	48 (7%)
4	42 (6%)
5	12 (2%)
6	1 (0%)
7	1 (0%)
8	1 (0%)

Dose Changes:

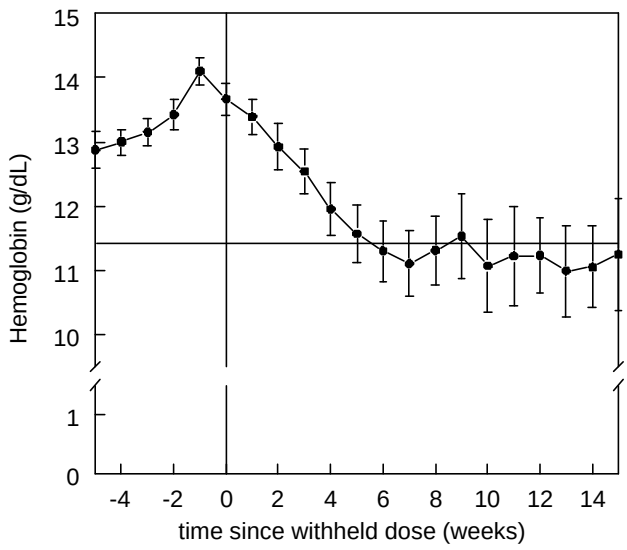
Of the 703 subjects in Study 140, 286 (40.7%) required no change in dose during the investigation. Approximately 28% of subjects had ≥ 1 reported dose decrease; 39% had ≥ 1 reported dose increase (Table 21). Fifty-two subjects (7%) had ARANESP withheld for Hgb >14 g/dL on one occasion, and 5 subjects (1%) had ARANESP withheld for Hgb > 14 g/dL on 2 occasions.

Effect of Withholding ARANESP:

ARANESP was to be withheld for Hgb >14 g/dL and was restarted when Hgb decreased to < 12 g/dL. Figure 15 shows the mean Hgb from 5 weeks before to 15 weeks

after a withheld dose(s) for 53 subjects who had ARANESP withheld for Hgb >14 g/dL. Dosing was withheld for the first time at a median of 12 weeks (range: 5 to 30 weeks) and the Hgb for these subjects returned to < 12 g/dL after a median of 4 weeks (range: 1 to 12 weeks).

Figure 15: Hgb Versus Time Relation After Withholding ARANESP – Study 140



Average Weekly ARANESP Dose:

The median ARANESP dose during the titration period was 30 μg/week (quartiles 19, 40 μg/week; range: 3.8–125 μg/week). The median weight-adjusted dose was 0.4 μg/kg/week. For the maintenance period, the median dose was unchanged; however, the range was wider (quartiles 20, 45 μg/week; range: 3–225 μg/week).

Relation Between Baseline EPO Dose and Final ARANESP Dose

CBER assessed the relations between baseline EPO dose and final ARANESP dose, for both weight-adjusted and non-weight-adjusted data. The respective dose-proportionalities, (i.e., the slopes of the regression lines), were 0.00387 μg ARANESP per unit EPO, and 0.00362 μg/kg ARANESP per unit/kg EPO. The reciprocals of the slopes are 258 units EPO per μg ARANESP and 276 units/kg EPO per μg/kg ARANESP, for weight-adjusted and non-weight-adjusted data. The R-values for both plots were the same (0.59), such that both offered comparable linear fits to the data.

Frequency of Dosing:

Most subjects (96.8%) who had been receiving thrice-weekly EPO were maintained on weekly ARANESP, and 96.6% of subjects who had been maintained on twice-weekly EPO were maintained on weekly ARANESP. Of subjects who had been receiving EPO only once weekly, 88.5% were maintained on QOW ARANESP. Seventeen (17) subjects (2.4%) received ARANESP on a BIW schedule, and 1 subject (0.1%) received ARANESP on a TIW schedule.

Safety:

At the interim analysis, this study encompasses ~330 subject-years of experience: 703 subjects received ARANESP, with a median exposure time of 24 weeks (range: 1–37 weeks). The mean weekly dose was 32 μg/week (range: 4–125) and the median weight-adjusted dose was 0.4 μg/kg/week.

Deaths:

There were 32 deaths on study and 4 deaths within 30 days of withdrawal, for an overall mortality rate of 5.1%. The leading cause of death was cardiac failure (6, 0.9%), followed by sudden death, cardiac arrest, malnutrition, and unknown (3 subjects; 0.4%, each).

Table 22: Reported Incidence of Serious and Non-Serious Adverse Events – Study 140

Number of Subjects	**703**		
Subjects reporting SAEs	245 (35%)		
SAEs with incidence ≥ 1.6%			
Thrombosis vascular access	24 (3.4%)		
Access stenosis	17 (2.4%)		
Fever	14 (2.0%)		
Hypertension	11 (1.6%)		
Dyspnea	11 (1.6%)		
Pulmonary edema	11 (1.6%)		
Subjects Reporting AEs	602 (86%)		
AEs with incidence ≥ 5%			
Myalgia	112 (16%)	Pain abdominal	46 (7%)
Hypertension	108 (15%)	Pain back	45 (6%)
Hypotension	106 (15%)	Arthralgia	43 (6%)
Headache	85 (12%)	Bronchitis	42 (6%)
Vomiting	78 (11%)	Dyspnea	40 (6%)
Upper respiratory infection	72 (10%)	Pain limb	39 (6%)
Diarrhea	67 (10%)	Influenza-like symptoms	36 (5%)
Injection site pain	60 (9%)	Pruritus	36 (5%)
Cough	56 (8%)	Fatigue	33 (5%)
Fever	52 (7%)	Thrombosis vascular access	33 (5%)
Nausea	47 (7%)	Access stenosis	32 (5%)

Adverse Events:

Adverse events are summarized in Table 22. Serious adverse events were reported in 245 subjects (35%). The most commonly reported SAE was TVA (3.4%), followed by access stenosis (2.4%) and fever (2.0%). Other SAEs with a reported incidence of 1.6% or greater were pulmonary edema, dyspnea and HTN (1.6%, each). Non-serious adverse events appear with typical frequency for a dialysis population with ESRD: myalgia, HTN, hypotension and headache were most common. The utility of the data is limited by the lack of a contemporaneous control group, and the high background level of AEs in the subject population. Additional analysis are found in CBER's integrated analysis of safety.

Doses Withheld:

Doses were withheld in 57 subjects (8.1%), of whom 53 had doses withheld because of Hgb ≥ 14 g/dL. No AEs were associated with the elevated Hgb concentration in 47 subjects. Of the remaining 6 subjects, 4 (0.6%) had doses withheld in association with serious, treatment-related AEs. One event each of convulsions, cerebrovascular accident, TVA and access stenosis were reported. Two subjects had a Hgb > 14 g/dL in the period before their death, but neither death was considered treatment-related. Dosing was withheld in 4 subjects when the Hgb was not >14 g/dL. One subject had ARANESP withheld for Hgb >13 g/dL (without reported associated AEs). Dosing was withheld during a period of hospitalization for Herpes encephalitis in 1 subject, due to impending death in another, and due to an allergic reaction in the third. None of these events was reported by the investigator as treatment-related.

Withdrawals Due to Adverse Events:

Adverse events contributing to withdrawal from the study were reported in 19 subjects (3%), and reported as treatment-related in 11. Six (6) subjects were withdrawn for AEs that led to death. One of these events, an intracranial hemorrhage, was reported as treatment-related. In 8 subjects, withdrawal was due to intolerable AEs, all of which were treatment-related. There were 2 cases of hypertension, 2 of pruritus, and 1 each of TVA, hypoglycemia, flu-like symptoms and injection site pain. Two additional subjects were withdrawn due to treatment-related HTN. Three others withdrew due to fatigue or unrelated medical conditions (pneumonia and malignancy). Nine subjects withdrew because of investigator/administrative decisions. These included 1 subject who was withdrawn at week 36 due to non-response to ARANESP despite increasing both the dose and frequency of administration (Hgb 7.5 g/dL at withdrawal). This subject, although iron replete at baseline (ferritin 145 ng/mL), had inadequate iron stores despite IV iron supplementation. Twenty subjects requested withdrawal, including 1 subject who had 3 SAEs of HTN. Five subjects requested withdrawal because of asthenia, fatigue, vertigo, pruritus, or "feeling unwell," and 4 additional subjects requested withdrawal because of AEs (angina, fatigue, headaches, and dizziness) believed to be due to low Hgb values.

RBC Transfusions:

Sixty-five (65) subjects (9%) received RBC transfusions. In 46, transfusions were associated with a decrease in Hgb that appeared to be related to an AE such as hemorrhage, thrombosis, infection, inflammation, or surgery. In 6 subjects, transfusions were administered either in preparation for or immediately after renal transplant. Thirteen (13) subjects were transfused for a low Hgb without an associated obvious, correctable cause.

Vital Signs:

The overall values for heart rate, and systolic and diastolic blood pressure were stable throughout the study, though there was considerable within-subject variation. A third of subjects had a maximum increase in systolic blood pressure of > 30 mmHg, and 40% had a maximum decrease of ≥ 30 mmHg. Thirty-seven (37) subjects (5%) had a maximum increase in diastolic blood pressure of ≥ 30 mmHg, and 50 (7%) had a maximum decrease of ≥ 30 mmHg. Such changes are not unexpected for a CRF patient population on dialysis.

Antihypertensive Medications:

There were numerous additions, subtractions and changes in anti-hypertensive medication use, but overall no suggestion that the study agent caused or exacerbated hypertension in this study population.

Chemistry Evaluations:

Abnormal laboratory findings were reported as AEs in 4 subjects. These were not considered treatment-related by investigators, and no other changes in values for any of the biochemistry variables were considered by investigators to be clinically significant. No notable shifts in values for any variable were observed.

Antibody Formation:

Post-baseline serum samples for antibody testing were available for 679 subjects at a median ARANESP exposure time of 25.5 weeks (range: 1 to 38 weeks). Samples were missing for 24 subjects, including 6 subjects without a baseline serum sample, and 18 subjects who withdrew

before week 12, and for whom a follow-up sample was not available. Antibody formation was not confirmed in any subject.

One subject had a single reactive sample at week 24 with subsequent negative results (weeks 12, 36 and 38). No further characterization was performed.

Results of Pharmacokinetic Substudy 980194:

Sixteen (16) subjects were enrolled; 4 withdrew and 12 completed the substudy. Two subjects were withdrawn at the end of Week 1 because they failed to meet inclusion criteria (receipt of ARANESP on a weekly schedule). One subject withdrew consent because of a low Hgb, and another was withdrawn after receiving a dose of EPO. An additional subject failed to provide data because of missing samples at Week 8, and another was excluded for apparent IV administration of ARANESP. There appeared to be a considerable disparity in the mean dose-normalized baseline-corrected ARANESP concentration-time profiles between Weeks 1 and 8, with the dose-dependent parameters (C_{max} and AUC) higher at Week 8 than Week 1. This was at least partially attributable to a single subject, who exhibited a serum ARANESP concentrations on Week 8 substantially higher than those of the other subjects.

Reviewer's Comments: The sponsor noted that the analysis showed that the CIs for all parameters, with the exception of MRT, included zero. Given the substantial variability and the limited sample size at Week 8, however, the strength of the evidence regarding similarity in parameters between weeks 1 and 8 is not substantial.

There was no apparent change in mean trough ARANESP concentrations between Week 1 and Week 8. This was true for both the dose-normalized and non-normalized trough concentrations.

Financial Disclosure:

No financial interests were disclosed by investigators in these studies.

Summary and Discussion:

The interim data from this ongoing, multicenter, uncontrolled safety study encompass ~700 subjects with a median time of 24 weeks on-study, and represent roughly one-third of the total clinical experience for ARANESP included in this application. The study directs that ARANESP is to be administered for 52 weeks; therefore, slightly less than half of the safety data are included in this submission.

Stable subjects with ESRD receiving HD or PD, with Hgb maintained on a stable regimen of EPO, were to be converted to ARANESP using a standard dose proportionality (200 U EPO → 1.0 µg ARANESP). The prior route of administration was to be maintained. Doses of ARANESP were titrated as necessary to maintain a target Hgb concentration in the range 9–13 g/dL and within -1.0 to +1.5 g/dL of the baseline Hgb concentration.

The median weekly dose of ARANESP was 30 μg (0.4 μg/kg), though there was considerable intra- and inter-subject variability. There were reported dose modifications in 59% of subjects through ~24 weeks of study. Despite these dose changes, ~28% of subjects exceeded the target Hgb of 13 g/dL, and Hgb values in excess of 14 g/dL were reported in 10% of subjects. These percentages would likely be substantially greater in an EPO-naïve patient population, that is

actually anemic at baseline, and for whom selection of an initial ARANESP dose could not be based on prior experience with another erythropoietin. This concern is further magnified because the study subjects were carefully monitored with protocol-driven ARANESP dose adjustments. In clinical practice, monitoring may be less rigorous and titration less precise, likely increasing the risk and/or extent of overshoot.

The CBER-calculated dose proportionality, based on the relation between baseline EPO dose and final ARANESP dose, suggested a conversion factor of 258–276 units EPO per μg ARANESP, somewhat higher than the proportionality used to estimate the starting dose (i.e., indicating a higher potency of ARANESP relative to EPO). The use of a higher proportionality factor for the starting dose (i.e., implying greater potency of ARANESP relative to EPO), could lead to a lower proportion of subjects who exceed the target Hgb.

For subjects who had ARANESP withheld due to a Hgb >14 g/dL, the Hgb decreased progressively and returned to within acceptable limits (< 12 g/dL) within a median of 4 weeks (range: 1 – 12 weeks).

The AE profile appeared to be consistent with that expected for a population of CRF subjects undergoing dialysis; however, the uncontrolled study design and the typically high background rate of AEs in this subject population limit the strength of the data. The study SAEs and AEs are reviewed comprehensively CBER's integrated analysis of safety. No confirmed antibody formation was detected for any subject in the study.

Mean blood pressure was stable throughout the study, although, as is typical for CRF subjects on dialysis, individual subjects showed considerable variation. There were no apparent trends in the use of anti-hypertensive medications.

With respect to the assessment of ARANESP safety, many of the limitations inherent in Studies 117 and 200 apply to Study 140, as well. These factors conspire to underestimate the risk inherent in initiating ARANESP in an anemic population with ESRD:

1. The study did not address the safety of ARANESP in *anemic* subjects. Initiation of erythropoietic therapies in anemic patients may impart potential risks related to expansion of extravascular volume with increased hemodynamic stress, as well as rheologic factors (i.e., alterations in blood viscosity). By design, Study 140 did not address the safety of ARANESP in this context.
2. The study was performed in a selected patient population, in that subjects could meet entrance criteria only if they had shown a stable response to EPO. Presumably, such subjects were more likely to respond predictably to ARANESP.
3. The baseline EPO dose was used to calculate the initial ARANESP dose. Thus, subjects who had been maintained on lower doses of EPO (i.e., with more limited EPO dose requirements and/or an enhanced sensitivity to EPO) would have had ARANESP initiated at a lower dose. Presumably, therefore, an overly rapid rate of rise in Hgb with its potential attendant risks would have been avoided in these subjects. In clinical practice, such information would be unavailable for EPO-naïve patients.

In addition, it should be pointed out that the study was conducted in Europe and Australia, and includes only a very limited number of subjects of African origin (3%). Moreover, only 5% of subjects were receiving PD in this study (95% were receiving HD).

From the standpoint of the efficacy of ARANESP, the data suggest that ARANESP maintains erythropoiesis in subjects with ESRD, previously receiving EPO therapy. The strength of the efficacy data are, to a fair extent, limited, because:

1. The study does not address to what extent, if any, the EPO administered to these subjects prior to study entry was actually efficacious. The study did not include a requirement for demonstration of the efficacy of EPO upon its initiation in individual subjects prior to the time of enrollment.
2. Subjects were not necessarily anemic when ARANESP was initiated.

In summary, the interim data from this ongoing study suggest that ARANESP administered weekly or biweekly, by the IV or SC route, maintains Hgb in subjects with CRF undergoing dialysis who were previously receiving EPO. The fact that 28% of subjects experienced Hgb values in excess of 13 g/dL is concerning, particularly because this fraction would likely be much higher in a population of CRF patients who are anemic at baseline, in whom selection of an initial ARANESP dose could not be guided by prior experience with another erythropoietin, and for whom the Hgb response may not be monitored as closely as in this clinical trial.

The investigation provides an additional safety experience with ARANESP; however, the strength of the study is limited by its uncontrolled design, as well as the limitations inherent in an investigation that simply converts stable, minimally-anemic subjects on a well-defined regimen of EPO to an alternative erythropoietic agent.

Study 160 – Phase 3, Chronic Safety Extension Study:

Title:	An Open-Label Study of the Long-Term Safety of ARANESP Therapy in Subjects With Chronic Renal Failure Receiving Dialysis Who Were Previously Enrolled in ARANESP Clinical Trials
Study Period:	May 1998 – ongoing; cutoff for interim analysis 6/30/99
Centers:	Twenty-four (24) centers in Europe (20) and Australia (4)
Subjects:	177 enrolled, up to 1000 to be enrolled
Notes:	This study is not being conducted under IND.

Objectives:

To evaluate the safety and tolerability of extended ARANESP treatment after 52 weeks of prior ARANESP treatment in subjects with CRF receiving dialysis.

Design:

This is a phase 3, multicenter, uncontrolled study to evaluate the long-term safety and tolerability of ARANESP. Upon completion of 52 weeks of participation in another ARANESP clinical trial, subjects could continue ARANESP therapy for ≤ 104 weeks. The route of administration is to match the route used in the previous clinical trial. Subjects previous treated with TIW ARANESP are to be switched to QW ARANESP, the total weekly dose was to remain unchanged. All other subjects are to continue treatment with their previous schedule of ARANESP administration. If necessary, the dose of ARANESP is to be adjusted by ± 25% of the starting dose to maintain a target Hgb concentration of 9 – 13 g/dL.

Safety is being assessed by the incidence of AEs, changes in laboratory variables and vital signs, and antibody formation to ARANESP. Laboratory measurements are performed at the local laboratory of each center. Complete blood counts and blood pressure are to be assessed monthly; serum chemistries and ARANESP antibodies are to be assessed every 3 months.

Study Population:

Adult subjects with CRF, who have completed 52 weeks of ARANESP therapy in a prior ARANESP study (ARANESP could be administered by the IV or SC route). Subjects with New York Heart Association class III or IV congestive heart failure, and subjects who are pregnant or breast-feeding are ineligible.

Study Endpoints:

Primary:
The primary endpoint is the incidence of AEs, with subgroup analyses planned to include: route of ARANESP administration, modality of dialysis, baseline Hgb, and age. No hypothesis-testing is planned.
Secondary:

- Hgb level; changes in Hgb
- dose and frequency of ARANESP administration
- vital signs; laboratory variables (hematology, chemistry, and iron levels)
- number and proportion of subjects receiving ≥ 1 RBC transfusion
- incidence of antibody formation

Interim Analyses:

Two interim analyses were planned: the first analysis included all subjects who had completed ≥ 12 weeks of ARANESP treatment on this study as of 6/30/99 and those who discontinued the study prematurely on or before that date. A second interim analysis is planned when all evaluable subjects have completed ≥ 52 weeks of treatment. Because no formal inferential tests are to be applied to the data, statistical adjustments for this interim analysis are not applicable.

Results:

Demographic and Other Baseline Characteristics:

The sponsor's interim analysis included 177 subjects, of whom 176 had received study agent and were included in the analyses of safety and efficacy (1 subject withdrew because of an impending renal transplant). The majority of subjects (83%) had rolled over from study ARANESP 970200, with the remainder continued from Studies 960245 and 960246.

Fifty-one percent (51%) of subjects were male, and 88% were Caucasian. Median age was 65 years (range: 23–89); median weight was 67.3 kg (range: 30–108). The majority of subjects (82%) were receiving HD, and 60% were receiving ARANESP by the SC route. At the time of study entry, 72% of all subjects were receiving QW ARANESP dosing, with 5%, 7% and 16% receiving ARANESP on BIW, TIW, and QOW schedules, respectively. The median ARANESP dose at study entry was 30 μg/wk (range: 3.8–200 μg/week). The mean baseline Hgb was 11.3 g/dL (range: 7.5–13.6). At baseline, 13 subjects were outside of the 9–13 g/dL target Hgb range: 5 subjects (3%) were below and 8 subjects (5%) were above range. Thirteen subjects changed from a TIW to QW dosing schedule upon enrollment into the study, as per protocol.

Protocol Deviations and Treatment Compliance:

Deviations from protocol were mostly minor and unlikely to affect study endpoints. These included 18 subjects who failed to provide informed consent prior to enrollment, 9 subjects who were late in changing their ARANESP administration schedule from TIW to QW, and 8 subjects with missing antibody assessments. At the time of the interim analysis, 19 subjects (11%) had withdrawn from study. Reasons for withdrawal included death (11 subjects), renal transplant (6 subjects) and AEs (2 subjects).

Efficacy:

Hgb was generally maintained within the target range, between baseline (week 52) and week 76. Beyond week 76, the interim data were too sparse to be meaningful. For each of the subgroups evaluated by the sponsor (route of administration, modality of dialysis, age, and subjects changing dosing schedule from TIW to QW), mean Hgb was maintained within the target range during this period.

The numbers of subjects with Hgb values within and outside the 9–13 g/dL target range are shown in Table 23. Combining data for weeks 56, 60 and 64, time-points at which data are substantially complete, ~4.5% of Hgb values were reported to be below the target range, and ~8.5% were above. On Week 56, 9.8% of subjects were reported to have Hgb values > 13 g/dL.

Reviewer's Comments: **Patients driven to high Hgb values may be exposed to excess risks of cardiovascular and CNS events. The sponsor reported a maximum of 9.8% of subjects with Hgb values >13 g/dL at Week 56. More importantly, with a median exposure time of 18 weeks, CBER calculated that 22.2% of subjects experienced a Hgb concentration in excess of 13 g/dL. This is a relatively high frequency, particularly because these subjects had been rolled over from other studies and had been previously titrated on ARANESP with stable regimens at enrollment. Given that the upper limit of the Hgb target range was 13 g/dL, this experience suggests that, for a stable patient population receiving chronic ARANESP therapy, a substantial fraction of patients may be expected to exceed the upper limit of the target range.**

Table 23: Hgb Values Within and Outside Target Range – Study 160

	n	<9 g/dL	Within Range	>13 g/dL
Baseline	**175**	5 (2.9%)	162 (92.6%)	8 (4.6%)
Week 56	**164**	7 (4.3%)	141 (86.0%)	16 (9.8%)
Week 60	**162**	10 (6.2%)	141 (87.0%)	11 (6.8%)
Week 64	**157**	4 (2.5%)	139 (88.5%)	14 (8.9%)
Week 68	**90**	5 (5.6%)	79 (87.8%)	6 (6.7%)
Week 72	**60**	3 (5.0%)	53 (88.3%)	4 (6.7%)
Week 76	**51**	2 (3.9%)	47 (92.2%)	2 (3.9%)
Week 80	**20**	1 (5.0%)	18 (90.0%)	1 (5.0%)
Week 84	**11**	2 (18.2%)	9 (81.8%)	0 (0.0%)
Week 88	**10**	0 (0.0%)	10 (100.0%)	0 (0.0%)
Week 92	**2**	1 (50.0%)	1 (50.0%)	0 (0.0%)
Week 96	**1**	0 (0.0%)	1 (100.0%)	0 (0.0%)
Week 100	**1**	0 (0.0%)	1 (100.0%)	0 (0.0%)

Thirteen subjects who were receiving TIW ARANESP on their previous study switched to QW dosing upon enrollment. For these subjects, mean Hgb was maintained within the 9–13 g/dL target range through 76 weeks of ARANESP therapy; however, the mean decreased over time. For the 7 subjects who reached week 76, the mean change in Hgb from Week 52 to Week 76 was -1.6 g/dL (95% CI: -3.1, -0.1).

Reviewer's Comment: Though only a small number of subjects were in

the initial TIW dosing subgroup, the data suggest that, for the same total dose of ARANESP, the biologic effect may be reduced by decreasing the frequency of administration from TIW to QW.

The median weekly ARANESP dose was 30 μg/week at baseline (week 52), and remained unchanged during weeks 53–64 and weeks 65–76. Beyond week 76, data were too sparse to draw meaningful conclusions.

ARANESP doses were withheld in 9 subjects (5%); 5 of these subjects (3%) had doses withheld for Hgb >14 g/dL. Overall, 20% of subjects had dose decreases, and 30% had dose increases.

Safety:

One hundred seventy-six (176) subjects received ARANESP, with a median exposure time of 18 weeks.

Adverse events:

Adverse events were reported in 81% of subjects, of which 29% were serious, 25% were regarded as severe and 4% were considered to be treatment-related. The most common AEs were vomiting (10%), hypertension and nausea (9% each), arthralgia and hypotension (8% each), and access infection, cough and headache (7% each). The sponsor's subgroup analyses of AEs by route of administration, modality of dialysis, baseline Hgb and age did not show any apparent difference in incidences of AEs.

Serious Adverse Events:

Serious adverse events were reported in 51 subjects (29%). The most common SAEs were cardiac failure (3%), and dyspnea, HTN, peritonitis and TVA (2% each).

Severe Adverse Events:

Forty-four subjects (25%) reported 1 or more AEs that were graded severe, life-threatening, or fatal. Eleven events occurred with an incidence of ≥2%: cardiac failure (3%), and angina, dyspnea, access infection, fever, hypertension, hypotension, peritonitis, hyperkalemia, myocardial infarction, and sepsis – each with an incidence of 2%.

Deaths:

There were 11 deaths on study and 2 deaths in subjects who died after being withdrawn from the study due to AEs. Reported causes of death were primarily cardiovascular (cardiac failure [3], myocardial infarction [2], cardiac arrest [1], pulmonary edema [1], cerebrovascular accident [1]), with additional deaths from multi-organ failure (2), renal failure (1), and bronchial carcinoma (1).

Reviewer's Comments: The total on-study experience through this interim analysis is 65.3 subject-years, and the death of 13 subjects represents an unadjusted annual mortality rate of roughly 20%, which is somewhat higher than expected for this patient population. (All deaths for the clinical development program will be considered together in CBER integrated analysis of safety.)

Withdrawals Due to Adverse Events:

There were 2 withdrawals due to AEs: one was for bronchial carcinoma and another for cerebral ischemia. Both subjects died within 28 days of withdrawal from study.

Vital Signs; Clinical Laboratory Evaluation:

No clinically significant changes in blood chemistry variables were reported by investigators, and no notable shifts in any biochemistry variable were observed. The mean systolic and diastolic blood pressure values at week 52 were 143 and 79 mm Hg, respectively, and at week 76 the systolic and diastolic BP values were 143 and 77 mm Hg, respectively.

Although the mean BP values remained stable throughout the study, there was considerable week to week variation in BP for individual subjects, with maximum upward shift in systolic ≥ 30 mm Hg reported in 32% of subjects, and downward shifts of ≥ 30 mm Hg reported in 22% of subjects.

RBC Transfusions:

Blood transfusions were reported in 22 subjects (13%). In 17, transfusions were associated with a decrease in Hgb that appeared to be related to an AE such as hemorrhage, infection, inflammation, anemia, or surgery. Five (5) subjects were transfused for low Hgb without obvious etiology.

ARANESP Antibodies:

There were 146 subjects with ≥ 76 weeks of follow-up, and13 subjects with ≥ 100 weeks of follow-up. All samples were seronegative for presence of anti-ARANESP antibodies.

Summary:

As of this interim analysis, the extent of ARANESP safety data collected for Study 160 is limited to a median exposure of 18 weeks, or ~65 subject-years of experience. (In contrast, as of its interim analysis, Study 140 has accumulated ~330 subject-years of experience.)

The overall safety data for this study were broadly comparable to those typical of a CRF patient population undergoing dialysis. CBER found 22.2% of subjects with reported Hgb values in excess of 13 g/dL. This is particularly concerning, because ARANESP doses had been carefully titrated during the course of previous studies, and median exposure time was only 18 weeks in this study. The experience of Hgb values in excess of the target range may place patients at risk of excess cardiovascular and CNS events (see CBER's integrated analysis of safety). For the limited number of subjects in whom the schedule of ARANESP administration was changed from TIW to QW (while the total ARANESP dose was unchanged), Hgb tended to decrease, suggesting that the biologic effect of ARANESP may be decreased by decreasing the frequency of administration.

Safety of ARANESP:

Potential ARANESP-related toxicities can be broadly categorized as those resulting from: 1) manifestations of exaggerated or poorly-controlled pharmacodynamic effects (i.e., excessive erythropoiesis); or 2) toxicities unrelated to the putative mechanism of action. The former are thought to have, as their basis, alterations in rheologic and/or hemodynamic factors, and include accelerated hypertension, congestive heart failure, pulmonary edema, ischemic events (stroke, TIA, acute MI, TVA, peripheral ischemia/gangrene), and seizures. No specific toxicities, unrelated to mechanism of action, had been identified for ARANESP in the pre-clinical program.

Characterization of the safety of ARANESP in this license application was not straightforward, because the substantive investigations in the ARANESP clinical development program were either

active-controlled or uncontrolled studies, and the vast majority of the experience was unblinded. Thus, a placebo control group was not incorporated into the development program, and the more subjective AEs were likely to be influenced by both subject and investigator biases. Moreover, AEs occur frequently in the CRF patient population, and AEs attributable to study agents were assessed against this background. Cardiovascular events, in particular, occur commonly in the CRF patient population, yet they also constitute the primary manifestation of excessive erythropoiesis, as noted above.

The clinical development program evaluated the use of ARANESP in 2 general settings applicable to the CRF population: 1) correction of anemia in EPO-naïve subjects (i.e., “correction” studies); and 2) as maintenance therapy for patients who had been previously treated with EPO (i.e., “conversion” studies). Subjects who had received ≥1 dose of study drug are included in these analyses. Overall, this includes safety data for 1598 ARANESP-treated subjects and 600 EPO-treated subjects. Results from 3 single-dose pharmacokinetic studies (980212, 960224 and 990134) are not included. Two (2) subjects randomized to EPO received ARANESP while on-study, and are included in the ARANESP group for the purpose of these analyses. The median lengths of exposure to study agent were 24 and 28 weeks for the ARANESP and EPO groups, respectively.

Demographics and Baseline Disease Status:

Table 24 provides an overview of subject demographics and baseline hematologic parameters. Overall, ARANESP- and EPO-treated subjects were well-matched for age (median age = 59 years for both groups) and gender (57% male).

The vast majority of ARANESP-treated subjects were Caucasian (83%), and there were lower percentages of subjects of African, Asian, Hispanic and Native American ancestry in the ARANESP group, relative to the EPO group. These imbalances were largely the result of a predominant number of European subjects in the ARANESP group (5/6 of ARANESP-treated subjects were enrolled at non-U.S. sites). Enrollment of subjects of African ancestry, in particular, was limited in the ARANESP group (11%). Mean body weight tended to be lower in the ARANESP group, and this, too, may have been related to the over-representation of European subjects in the ARANESP group. Baseline Hgb tended to be slightly lower in the ARANESP group, in that 25% of subjects had a baseline Hgb < 10 g/dL, as compared to 14% of such subjects in the EPO group. Subjects were reasonably well-matched for iron status between the treatment groups.

Table 24: Baseline Demographic and Hematologic Characteristics

	ARANESP	EPO
	n = 1598	n = 600
Age [years]		
Mean	59.1	58.7
Median	62	60
SD	15.1	15.4
Quartiles	49 - 71	49 - 71
Range	18 - 91	21 - 90
Age Category [n (%)]		
< 65	923 (58%)	353 (59%)
65 - 75	436 (27%)	160 (27%)
>= 75	239 (15%)	87 (15%)
Gender [n (%)]		
Female	691 (43%)	261 (43%)
Male	907 (57%)	339 (57%)
Race [n (%)]		
Caucasian	1321 (83%)	367 (61%)
African descent	172 (11%)	156 (26%)
Asian	53 (3.3%)	34 (5.7%)
Hispanic	23 (1.4%)	32 (5.3%)
Native American	3 (0.2%)	4 (0.7%)
Other	26 (1.6%)	7 (1.2%)
Subject Mass [kg]		
Mean	70.7	73.9
Median	69.4	71.5
SD	15.9	20.2
Range	31.5 - 158	35 - 188
Subject Mass Tertiles [n (%)]		
< 63 kg	530 (33%)	177 (30%)
63 - 76 kg	536 (34%)	181 (30%)
>=76 kg	525 (33%)	241 (40%)
Hgb [g/dL]		
Mean	10.59	10.90
Median	10.80	11.00
SD	1.24	1.00
Quartiles	10.0 - 11.5	10.35 - 11.65
Range	5.2 - 12.5	6.1 - 12.6
Hgb [n (%)]		
< 10 g/dL	397 (25%)	86 (14%)
10 - 11.5 g/dL	827 (52%)	334 (56%)
> 11.5 g/dL	374 (23%)	180 (30%)
Ferritin (ng/mL)		
Mean	390	403
Median	312	316
SD	298	317
Quartiles	187 - 504	178 - 522
Range	12 - 3082	18 - 1931
Transferrin Saturation (%)		
Mean	31.0	32.3
Median	27.7	29
SD	13.3	12.2
Quartiles	23 - 35	24 - 37
Range	4 - 117	16 - 92

Table 25 provides a summary of dialysis modality, treatment route, and treatment frequency. The many disparities largely reflect differences between the various protocol designs. The ARANESP study population includes data from HD (84%), PD (8%), and predialysis (8%) subjects. ARANESP-treated subjects were fairly equally divided between the IV (47%) and SC (53%) routes of administration. The frequency of ARANESP administration ranged from TIW to QOW, but was generally weekly (81%); EPO was generally administered thrice-weekly (77%).

Table 25: Baseline Dialysis-Modality, Study Agent Route and Schedule

	ARANESP	EPO
	n = 1598	n = 600
Dialysis Modality		
Hemodialysis	1343 (84.0%)	537 (89.5%)
Peritoneal Dialysis	126 (7.9%)	26 (4.3%)
Pre-Dialysis	129 (8.1%)	37 (6.2%)
Treatment Route		
IV route	745 (46.6%)	437 (72.8%)
SC route	853 (53.4%)	163 (27.2%)
Treatment Frequency		
Weekly	1302 (81.5%)	35 (5.8%)
Twice weekly	1 (0.1%)	104 (17.3%)
Thrice Weekly	75 (4.7%)	461 (76.8%)
Every other week	220 (13.8%)	0 (0%)

Differences in study designs and randomization paradigms led to some interesting and potentially important imbalances between the ARANESP and EPO study groups (Table 26). Roughly four-fifths of the clinical experience with ARANESP was in subjects who were converted from EPO. Thus, the safety of ARANESP in the context of CRF and *anemia* was assessed in only one-fifth of subjects (n = 348). Approximately half of all ARANESP-treated subjects were enrolled in active-controlled studies, but only 11% were enrolled in a double-blind study (Study 117 was the sole source of such subjects). Finally, whereas EPO-treated subjects were fairly evenly divided between U.S. and non-U.S. sites, the preponderance of ARANESP-treated subjects were enrolled outside the U.S (83%). Thus, *disparities in practices for the reporting of AEs between U.S. and non-U.S. sites could differentially affect the apparent rates of AEs in ARANESP- and EPO-treated subjects.*

Table 26: Study Populations by Use of Study Agent, Study Design, and Geographic Location (U.S.; Non-U.S.)

	ARANESP	EPO
	n = 1598	n = 600
Use of Agent		
Correction of Anemia	348 (21.8%)	77 (12.8%)
Conversion from EPO	1250 (78.2%)	523 (87.2%)
Controlled/Uncontrolled Study		
Controlled	823 (51.5%)	600 (100%)
Uncontrolled	775 (48.5%)	0 (0%)
Blinded/Open Label Study		
Blinded	169 (10.6%)	335 (55.8%)
Open-label	1429 (89.4%)	265 (44.2%)
U.S./Non-U.S.		
U.S.	267 (16.7%)	333 (55.6%)
non-U.S.	1331 (83.3%)	267 (44.5%)

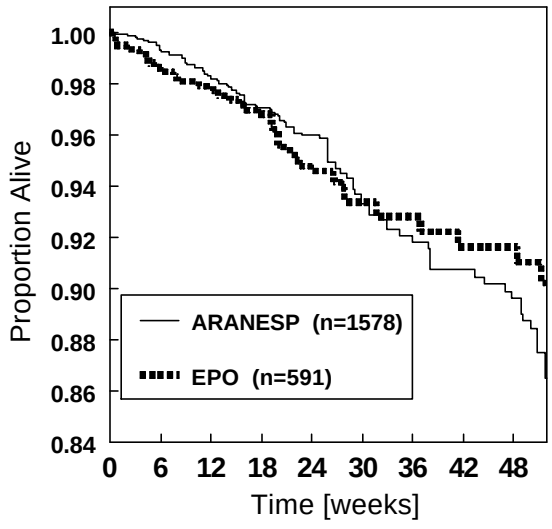
The overall disposition of subjects for the safety analyses is summarized in Table 27. A total of 21% of ARANESP-treated subjects and 17% of EPO-treated subjects discontinued from study. Deaths and renal transplantation were the leading causes of withdrawal in both groups. The frequency of death was similar in the two groups, with 100 deaths (6.3%) in the ARANESP group and 33 (5.5%) in the EPO group.

Table 27: Subject Disposition

	ARANESP	EPO
Received Study Agent	**n = 1598**	**n = 600**
Discontinued	**343 (21.5%)**	**99 (16.5%)**
Death on Study	100 (6.3%)	33 (5.5%)
Kidney Transplant	104 (6.5%)	21 (3.5%)
Withdrawal Requested	48 (3.0%)	13 (2.2%)
Intolerable Adverse Event	35 (2.2%)	21 (3.5%)
Administrative/Investigator Decision	40 (2.5%)	8 (1.3%)
Lost to Follow-Up	7 (0.4%)	1 (0.2%)
Unrelated Medical Condition	4 (0.3%)	1 (0.2%)
Other	4 (0.3%)	0 (0%)
Protocol Violation	1 (0.1%)	0 (0%)
Change in Dialysis Modality	0 (0%)	1 (0.2%)
Completed Study	**373 (23.3%)**	**466 (77.7%)**
Ongoing	**882 (55.2%)**	**35 (5.8%)**

CBER performed a time-to-event (Kaplan-Meier) analysis for death for the data originally submitted in the BLA (i.e., interim data from Studies 211 and 202, including 1578 ARANESP-treated and 591 EPO-treated subjects, Figure 16), and there was no significant difference in time-to-event between groups. Given the relatively small numbers of subjects that would be added by incorporating additional data from these studies (ARANESP: 2 deaths in 20 subjects, EPO: no deaths in 9 subjects), this analyses were not repeated.

Figure 16: Percent Survival in All Studies – Kaplan-Meier Analysis



Adverse Events:

The sponsor's analyses of AEs were found to be unreliable, and were not used as the basis for this review. There were two primary deficiencies in the sponsor's analyses:

1. Upon examination the AE line listings within the SAS transport files, CBER found a substantial number of AEs that had been incorrectly or incompletely classified/mapped. Moreover, in some cases, closely related AEs were divided into different categories (e.g., edema, peripheral edema, genital edema, etc.), which decreased the power of the analyses. Together, these factors led to the underestimation of the rates of a number of AEs, including infection, congestive

heart failure, angina, arrhythmia, edema, and others. CBER's concerns were communicated to Amgen, and the sponsor largely concurred with CBER's reclassification and edited mapping of line listings.

2. CBER's Complete Review letter of December 15, 2000 requested submission of final data from Studies 211 and 202. Though the sponsor submitted updated AE data files for Studies 211 and 202, these data were not combined with the data previously submitted from the other studies, and an updated integrated analysis of safety, based on final data from Studies 211 and 202, was not submitted.

Thus, the following tables and discussion are based on CBER's analyses of <u>edited</u> AE line listings from SAS transport files, and include updated data from the final datasets of Studies 211 and 202.

All Adverse Events – Comparison of Event Rates Between ARANESP and EPO:

Adverse events are listed in order of decreasing frequency in Table 28. CBER combined terms wherein there was a clear pathophysiologic relationship (e.g., dyspnea and tachypnea; volume overload, pulmonary edema, and CHF, etc.), and/or when the distinction between events would be expected to be ambiguous (e.g., URI and rhinitis; edema and peripheral edema, etc.).

For some AEs, small to moderate differences in frequencies are apparent between groups; however, disparities must be considered in light of the multiplicity of analyses. Moreover, the overall clinical experience was not randomized (nearly half of ARANESP-treated subjects were enrolled in uncontrolled studies); therefore, direct comparisons of rates between treatment groups is not valid. In general, however, there was a trend towards lower AE rates in ARANESP-treated subjects. A major exception to this trend was injection site pain, which was reported ~13 times more frequently in ARANESP-treated subjects than the EPO-treated subjects. Interestingly, however, *none* of the 169 subjects who received ARANESP in Study 117, the only double-bind study, reported injection site pain.

CBER assessed the frequencies of these AEs by subgroups of gender, race, age (<65, ≥ 65 to 74, >74), weight tertiles (<63, ≥63 to <76, ≥76 kg), route and frequency of study agent administration, study design (correction/conversion; open-label/blinded), and modality of dialysis (table not shown). The only concerning trend apparent was excess hypertensive events in subjects of African descent. In this subgroup, hypertension was reported as an AE in 59/172 ARANESP-treated subjects (34%), and 38/156 EPO-treated subjects (24%), raising the possibility of enhanced susceptibility to ARANESP-induced hypertension in patients of African origin.

With the above exception, the AE subgroup analyses do not raise particular concerns regarding the safety of ARANESP in patients with CRF, *relative to the safety of EPO*, though the limitations noted above must be borne in mind (i.e., multiplicity of analyses and non-randomized data).

Incidences of HTN, AMI, Stroke, Seizure, TIA and TVA:

The sponsor identified 6 events of particular importance in patients with ESRD receiving erythropoietins: HTN, acute MI, cerebrovascular disorder, seizures, TIA, and TVA. The incidences of these events are summarized by subgroup of gender, race, age, weight, route of administration, study blinding, use (correction, maintenance) and mode of dialysis in Table 29.

Table 28: Adverse Events by Decreasing Frequency

	ARANESP	EPO		ARANESP	EPO
N (%)	1598	600	N (%)	1598	600
infection	617 (0.39)	254 (0.42)	epistaxis	54 (0.03)	23 (0.04)
nausea/ vomiting	376 (0.24)	195 (0.33)	rash	54 (0.03)	22 (0.04)
hypertension	374 (0.23)	157 (0.26)	peripheral ischemia	52 (0.03)	15 (0.03)
hypotension	362 (0.23)	148 (0.25)	fall	51 (0.03)	31 (0.05)
myalgia	328 (0.21)	160 (0.27)	pneumonia	50 (0.03)	28 (0.05)
URI, rhinitis	317 (0.2)	173 (0.29)	vertigo	46 (0.03)	9 (0.02)
access complication (excluding infection, TVA)	281 (0.18)	172 (0.29)	peritonitis	43 (0.03)	3 (0.01)
diarrhea	250 (0.16)	131 (0.22)	syncope	40 (0.03)	18 (0.03)
headache	263 (0.16)	111 (0.19)	gengrene, ischemic necrosis	34 (0.02)	15 (0.03)
edema	224 (0.14)	152 (0.25)	hypovolemia	33 (0.02)	7 (0.01)
arthralgia, arthritis	214 (0.13)	102 (0.17)	asthma wheeze	31 (0.02)	22 (0.04)
asthenia, fatigue	211 (0.13)	104 (0.17)	hyperkalemia	30 (0.02)	9 (0.02)
cough	206 (0.13)	100 (0.17)	acute MI	29 (0.02)	13 (0.02)
dyspnea tachypnea	199 (0.12)	105 (0.18)	ocular hemorrhage	29 (0.02)	8 (0.01)
volume overload, pulmonary edema, CHF	189 (0.12)	88 (0.15)	thrombotic events	28 (0.02)	9 (0.02)
abdominal pain	186 (0.12)	100 (0.17)	neoplasm	25 (0.02)	13 (0.02)
fever, rigors	174 (0.11)	69 (0.12)	allergic RXN	24 (0.02)	10 (0.02)
pain limb	158 (0.1)	92 (0.15)	palpit	23 (0.01)	7 (0.01)
arrhythmia	148 (0.09)	92 (0.15)	depression	22 (0.01)	16 (0.03)
impaired consciousness, ataxia, hypertonia, hypo/paresthesia	146 (0.09)	74 (0.12)	seizure	22 (0.01)	10 (0.02)
angina/CAD	137 (0.09)	53 (0.09)	hyperparathyroidism	21 (0.01)	18 (0.03)
TVA	133 (0.08)	87 (0.15)	GI ulcer	20 (0.01)	6 (0.01)
pruritus	132 (0.08)	46 (0.08)	cardiac arrest	18 (0.01)	9 (0.02)
pain back	131 (0.08)	72 (0.12)	stroke	18 (0.01)	8 (0.01)
dizziness	130 (0.08)	91 (0.15)	abscess	18 (0.01)	7 (0.01)
injection site pain	111 (0.07)	3 (0.01)	pleural effusion	17 (0.01)	6 (0.01)
access infection	108 (0.07)	39 (0.07)	resp failure	13 (0.01)	2 (0)
fluid overload	107 (0.07)	52 (0.09)	cachexia	10 (0.01)	3 (0.01)
infuenza-like symptoms	95 (0.06)	47 (0.08)	cerebral ischemia	9 (0.01)	0 (0)
CHF	93 (0.06)	29 (0.05)	alopecia	8 (0.01)	5 (0.01)
hemorrhage, hematoma	91 (0.06)	36 (0.06)	TIA	7 (0)	3 (0.01)
constipation	84 (0.05)	50 (0.08)	pancreatitis	6 (0)	4 (0.01)
confusion, agitation, anxiety	82 (0.05)	48 (0.08)	pericardiits	6 (0)	2 (0)
malaise	73 (0.05)	38 (0.06)	ICH	6 (0)	1 (0)
anorexia	70 (0.04)	36 (0.06)	injection site hemorrhage	5 (0)	3 (0.01)
sepsis, bacteremia	64 (0.04)	24 (0.04)	transplant rejection	5 (0)	0 (0)
GI bleed	64 (0.04)	22 (0.04)	hypoglycemia	4 (0)	2 (0)
dyspepsia	63 (0.04)	39 (0.07)	pulm embolism	4 (0)	1 (0)
anemia, worsened	63 (0.04)	35 (0.06)	sudden death	4 (0)	0 (0)
skin ulceration	63 (0.04)	21 (0.04)	COPD	3 (0)	3 (0.01)
pulmonary edema congestion	60 (0.04)	32 (0.05)	apnea	3 (0)	0 (0)
insomnia, sleep disorder	58 (0.04)	34 (0.06)	suicide	2 (0)	1 (0)
			SAH	2 (0)	0 (0)

Table 29: Frequency of HTN, Acute MI, Stroke, Seizure, TIA and TVA by Subgroup [number of events (frequency)]

Subgroup	group	N	Hypertension	Acute MI	Stroke	Seizure	Transient Ischemic Attack	Thrombosis of Vascular Access
Total		2198	531 (0.24)	42 (0.02)	26 (0.01)	32 (0.01)	10 (0)	220 (0.1)
All subjects	ARANESP	1598	374 (0.23)	29 (0.02)	18 (0.01)	22 (0.01)	7 (0)	133 (0.08)
	EPO	600	157 (0.26)	13 (0.02)	8 (0.01)	10 (0.02)	3 (0.01)	87 (0.15)
Male	ARANESP	907	211 (0.23)	19 (0.02)	10 (0.01)	12 (0.01)	2 (0)	70 (0.08)
	EPO	339	90 (0.27)	6 (0.02)	6 (0.02)	3 (0.01)	1 (0)	43 (0.13)
Female	ARANESP	691	163 (0.24)	10 (0.01)	8 (0.01)	10 (0.01)	5 (0.01)	63 (0.09)
	EPO	261	67 (0.26)	7 (0.03)	2 (0.01)	7 (0.03)	2 (0.01)	44 (0.17)
Caucasian	ARANESP	1321	285 (0.22)	22 (0.02)	16 (0.01)	15 (0.01)	6 (0)	94 (0.07)
	EPO	367	91 (0.25)	5 (0.01)	5 (0.01)	3 (0.01)	2 (0.01)	40 (0.11)
African descent	ARANESP	172	59 (0.34)	3 (0.02)	2 (0.01)	6 (0.03)	0 (0)	30 (0.17)
	EPO	156	38 (0.24)	7 (0.04)	3 (0.02)	6 (0.04)	0 (0)	33 (0.21)
Asian	ARANESP	52	11 (0.21)	2 (0.04)	0 (0)	0 (0)	0 (0)	2 (0.04)
	EPO	34	10 (0.29)	0 (0)	0 (0)	1 (0.03)	1 (0.03)	4 (0.12)
Hispanic	ARANESP	23	12 (0.52)	1 (0.04)	0 (0)	1 (0.04)	0 (0)	2 (0.09)
	EPO	32	15 (0.47)	1 (0.03)	0 (0)	0 (0)	0 (0)	5 (0.16)
Age <65	ARANESP	923	233 (0.25)	10 (0.01)	5 (0.01)	13 (0.01)	1 (0)	85 (0.09)
	EPO	353	103 (0.29)	8 (0.02)	1 (0)	5 (0.01)	2 (0.01)	55 (0.16)
Age 65-74	ARANESP	436	93 (0.21)	15 (0.03)	8 (0.02)	7 (0.02)	3 (0.01)	26 (0.06)
	EPO	160	37 (0.23)	3 (0.02)	1 (0.01)	4 (0.03)	1 (0.01)	21 (0.13)
Age >74	ARANESP	239	48 (0.2)	4 (0.02)	5 (0.02)	2 (0.01)	3 (0.01)	22 (0.09)
	EPO	87	17 (0.2)	2 (0.02)	6 (0.07)	1 (0.01)	0 (0)	11 (0.13)
Weight <63	ARANESP	530	130 (0.25)	11 (0.02)	4 (0.01)	11 (0.02)	3 (0.01)	40 (0.08)
	EPO	177	48 (0.27)	6 (0.03)	3 (0.02)	6 (0.03)	2 (0.01)	23 (0.13)
Weight 63-76	ARANESP	536	131 (0.24)	12 (0.02)	6 (0.01)	6 (0.01)	2 (0)	29 (0.05)
	EPO	181	55 (0.3)	3 (0.02)	2 (0.01)	2 (0.01)	1 (0.01)	23 (0.13)
Weight >=76	ARANESP	532	113 (0.21)	6 (0.01)	8 (0.02)	5 (0.01)	2 (0)	64 (0.12)
	EPO	242	54 (0.22)	4 (0.02)	3 (0.01)	2 (0.01)	0 (0)	41 (0.17)
IV route	ARANESP	745	170 (0.23)	13 (0.02)	6 (0.01)	10 (0.01)	4 (0.01)	91 (0.12)
	EPO	437	107 (0.24)	13 (0.03)	6 (0.01)	8 (0.02)	2 (0)	75 (0.17)
SC route	ARANESP	853	204 (0.24)	16 (0.02)	12 (0.01)	12 (0.01)	3 (0)	42 (0.05)
	EPO	163	50 (0.31)	0 (0)	2 (0.01)	2 (0.01)	1 (0.01)	12 (0.07)
open-label	ARANESP	1429	326 (0.23)	25 (0.02)	17 (0.01)	20 (0.01)	5 (0)	105 (0.07)
	EPO	265	77 (0.29)	3 (0.01)	4 (0.02)	4 (0.02)	2 (0.01)	27 (0.1)
blinded	ARANESP	169	48 (0.28)	4 (0.02)	1 (0.01)	2 (0.01)	2 (0.01)	28 (0.17)
	EPO	335	80 (0.24)	10 (0.03)	4 (0.01)	6 (0.02)	1 (0)	60 (0.18)
correction	ARANESP	348	102 (0.29)	9 (0.03)	4 (0.01)	4 (0.01)	1 (0)	25 (0.07)
	EPO	77	25 (0.32)	0 (0)	0 (0)	1 (0.01)	0 (0)	6 (0.08)
conversion	ARANESP	1250	272 (0.22)	20 (0.02)	14 (0.01)	18 (0.01)	6 (0)	108 (0.09)
	EPO	523	132 (0.25)	13 (0.02)	8 (0.02)	9 (0.02)	3 (0.01)	81 (0.15)
HD	ARANESP	1343	293 (0.22)	25 (0.02)	14 (0.01)	20 (0.01)	7 (0.01)	130 (0.1)
	EPO	537	139 (0.26)	13 (0.02)	7 (0.01)	10 (0.02)	3 (0.01)	86 (0.16)
PD	ARANESP	126	40 (0.32)	3 (0.02)	4 (0.03)	2 (0.02)	0 (0)	3 (0.02)
	EPO	26	10 (0.38)	0 (0)	1 (0.04)	0 (0)	0 (0)	0 (0)
pre-dialysis	ARANESP	129	41 (0.32)	1 (0.01)	0 (0)	0 (0)	0 (0)	0 (0)
	EPO	37	8 (0.22)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.03)

The frequency of HTN as a reported AE was similar in both ARANESP and EPO treatment groups. This was true across all subgroups of these studies, with three exceptions:

- As noted above, for subjects of African descent, HTN was reported as an AE in 34% of subjects in the ARANESP group, and 24% of subjects in the EPO group, raising the possibility of enhanced susceptibility to ARANESP-induced HTN in patients of African descent.

- HTN was reported as an AE in ~50% of Hispanic subjects in both treatment groups, though the overall experience in Hispanic subjects was quite limited.

- HTN was more frequently reported as an AE in subjects who were receiving a study agent to correct anemia, as compared to those who were converted from maintenance EPO. The frequency of HTN was similar in the ARANESP and EPO groups, however.

The frequency of TVA was similar between ARANESP- and EPO-treated subjects across all subgroups, and for the most relevant subgroup (subjects receiving HD), the incidence of TVA tended to be lower in subjects in the ARANESP-treated subjects (10%) than EPO-treated subjects (16%). Reports of acute MI, stroke, seizure and TIA were infrequent, and no conclusions can be drawn in terms of relative rates in the ARANESP and EPO groups (Table 29). CBER performed a similar analysis by duration of exposure to study agent for these events and subgroups (i.e., AEs expressed as events/unit time on study agent exposure), and the results were generally consistent.

Serious Adverse Events:

Serious adverse events with reported subject incidence >0.5% are shown over the entire safety database in Table 30 (without subgroup analyses), and SAEs with reported frequency >2.5% are shown by subgroup in Table 31. Events are presented by decreasing frequency in the ARANESP group. Subgroups for Table 31 include gender, race, age, weight, route of administration, blinding (open-label, blinded), use (correction, maintenance), and mode of dialysis. Note that TVA, access infection and access complications (other than infection and TVA) are of particular relevance for the HD subgroups. There are no trends suggesting excess risk of ARANESP relative to EPO in any subgroup. One possible exception was the apparent excess of infection and sepsis in Asian subjects. However, the difference is notable, not for a higher than expected frequency of events in ARANESP-treated subjects, but for a lower than expected frequency in subjects randomized to EPO. In the latter subgroup, the sample size is too small to draw meaningful conclusions (N=34).

Table 30: SAEs With Incidence >0.5% in the ARANESP Group

Event n (%)	ARANESP N=1598	EPO N=600
infection	210 (13.1)	68 (11.3)
TVA (HD only)	73 (5.4)	38 (7.1)
CHF	68 (4.3)	23 (3.8)
sepsis	56 (3.5)	17 (2.8)
arrhythmia	54 (3.4)	32 (5.3)
angina, CAD	46 (2.9)	19 (3.2)
access complication (excluding infection and TVA, HD only)	45 (3.4)	27 (5.0)
dyspnea tachypnea	40 (2.5)	13 (2.2)
access infection	38 (2.4)	8 (1.3)
HTN	36 (2.3)	5 (0.8)
pneumonia	35 (2.2)	19 (3.2)
pulmonary edema	35 (2.2)	13 (2.2)
fluid overload	33 (2.1)	10 (1.7)
GI bleed	33 (2.1)	7 (1.2)
fever, rigors	30 (1.9)	5 (0.8)
acute MI	29 (1.8)	11 (1.8)
gengrene, ischemic necrosis	28 (1.8)	11 (1.8)
nausea/ vomiting	27 (1.7)	10 (1.7)
peritonitis	24 (1.5)	2 (0.3)
abdominal pain	21 (1.3)	10 (1.7)
neoplasm	20 (1.3)	9 (1.5)
hypotension	19 (1.2)	9 (1.5)
diarrhea	19 (1.2)	6 (1.0)
cardiac arrest	18 (1.1)	9 (1.5)
stroke	18 (1.1)	7 (1.2)
peripheral ischemia	18 (1.1)	5 (0.8)
confusion, agitation, anxiety	18 (1.1)	3 (0.5)
skin ulceration	17 (1.1)	6 (1.0)
anemia, worsened	16 (1.0)	4 (0.7)
seizure	14 (0.9)	5 (0.8)
hemorrhage, hematoma	14 (0.9)	4 (0.7)
thrombotic events	12 (0.8)	6 (1.0)
hyperkalemia	11 (0.7)	5 (0.8)
syncope	11 (0.7)	4 (0.7)
asthenia, fatigue	11 (0.7)	3 (0.5)
respiratory failure	11 (0.7)	2 (0.3)
GI ulcer	10 (0.6)	1 (0.2)
abscess	10 (0.6)	0 (0)
cachexia	9 (0.6)	2 (0.3)
cerebral ischemia	9 (0.6)	0 (0)
headache	9 (0.6)	0 (0)
arthralgia/ arthritis	8 (0.5)	5 (0.8)
hypovolemia	8 (0.5)	2 (0.3)

Table 31: Serious Adverse Events by Subgroup – Reported Frequency > 2.5% [number of events (frequency)]

Subgroup	Group	N	infection	TVA	CHF	sepsis	arrhythmia	access complication (excluding infection and TVA)	angina, CAD	dyspnea tachypnea
Total		2198	278 (12.6)	114 (5.2)	91 (4.1)	73 (3.3)	86 (3.9)	78 (3.5)	65 (3)	53 (2.4)
All Subjects	ARANESP	1598	210 (13.1)	75 (4.7)	68 (4.3)	56 (3.5)	54 (3.4)	51 (3.2)	46 (2.9)	40 (2.5)
	EPO	600	68 (11.3)	39 (6.5)	23 (3.8)	17 (2.8)	32 (5.3)	27 (4.5)	19 (3.2)	13 (2.2)
male	ARANESP	907	129 (14.2)	42 (4.6)	37 (4.1)	35 (3.9)	33 (3.6)	26 (2.9)	23 (2.5)	20 (2.2)
	EPO	339	37 (10.9)	21 (6.2)	10 (2.9)	12 (3.5)	16 (4.7)	18 (5.3)	13 (3.8)	8 (2.4)
female	ARANESP	691	81 (11.7)	33 (4.8)	31 (4.5)	21 (3)	21 (3)	25 (3.6)	23 (3.3)	20 (2.9)
	EPO	261	31 (11.9)	18 (6.9)	13 (5)	5 (1.9)	16 (6.1)	9 (3.4)	6 (2.3)	5 (1.9)
Caucasian	ARANESP	1321	162 (12.3)	60 (4.5)	53 (4)	40 (3)	45 (3.4)	44 (3.3)	39 (3)	36 (2.7)
	EPO	367	43 (11.7)	24 (6.5)	13 (3.5)	10 (2.7)	20 (5.4)	17 (4.6)	11 (3)	7 (1.9)
Black	ARANESP	172	31 (18)	11 (6.4)	13 (7.6)	14 (8.1)	6 (3.5)	5 (2.9)	2 (1.2)	4 (2.3)
	EPO	156	22 (14.1)	9 (5.8)	6 (3.8)	7 (4.5)	9 (5.8)	7 (4.5)	6 (3.8)	6 (3.8)
Asian	ARANESP	52	10 (19.2)	1 (1.9)	1 (1.9)	2 (3.8)	2 (3.8)	0 (0)	4 (7.7)	0 (0)
	EPO	34	1 (2.9)	2 (5.9)	2 (5.9)	0 (0)	3 (8.8)	2 (5.9)	1 (2.9)	0 (0)
Hispanic	ARANESP	23	2 (8.7)	0 (0)	0 (0)	0 (0)	1 (4.3)	0 (0)	1 (4.3)	0 (0)
	EPO	32	2 (6.3)	2 (6.3)	2 (6.3)	0 (0)	0 (0)	1 (3.1)	0 (0)	0 (0)
Age <65	ARANESP	923	112 (12.1)	45 (4.9)	19 (2.1)	33 (3.6)	22 (2.4)	23 (2.5)	19 (2.1)	19 (2.1)
	EPO	353	28 (7.9)	25 (7.1)	11 (3.1)	7 (2)	12 (3.4)	16 (4.5)	9 (2.5)	7 (2)
Age 65-74	ARANESP	436	65 (14.9)	14 (3.2)	35 (8)	13 (3)	22 (5)	14 (3.2)	19 (4.4)	14 (3.2)
	EPO	160	25 (15.6)	8 (5)	8 (5)	4 (2.5)	14 (8.8)	7 (4.4)	7 (4.4)	3 (1.9)
Age >74	ARANESP	239	33 (13.8)	16 (6.7)	14 (5.9)	10 (4.2)	10 (4.2)	14 (5.9)	8 (3.3)	7 (2.9)
	EPO	87	15 (17.2)	6 (6.9)	4 (4.6)	6 (6.9)	6 (6.9)	4 (4.6)	3 (3.4)	3 (3.4)
Wt <63	ARANESP	530	63 (11.9)	23 (4.3)	25 (4.7)	19 (3.6)	16 (3)	18 (3.4)	13 (2.5)	14 (2.6)
	EPO	177	22 (12.4)	13 (7.3)	6 (3.4)	5 (2.8)	13 (7.3)	10 (5.6)	5 (2.8)	5 (2.8)
Wt 63 - 76	ARANESP	536	70 (13.1)	20 (3.7)	26 (4.9)	12 (2.2)	25 (4.7)	16 (3)	14 (2.6)	11 (2.1)
	EPO	181	18 (9.9)	6 (3.3)	9 (5)	6 (3.3)	7 (3.9)	6 (3.3)	9 (5)	2 (1.1)
Wt >=76	ARANESP	532	77 (14.5)	32 (6)	17 (3.2)	25 (4.7)	13 (2.4)	17 (3.2)	19 (3.6)	15 (2.8)
	EPO	242	28 (11.6)	20 (8.3)	8 (3.3)	6 (2.5)	12 (5)	11 (4.5)	5 (2.1)	6 (2.5)
IV route	ARANESP	745	98 (13.2)	47 (6.3)	30 (4)	35 (4.7)	28 (3.8)	18 (2.4)	19 (2.6)	14 (1.9)
	EPO	437	53 (12.1)	31 (7.1)	18 (4.1)	12 (2.7)	22 (5)	19 (4.3)	15 (3.4)	10 (2.3)
SC route	ARANESP	853	112 (13.1)	28 (3.3)	38 (4.5)	21 (2.5)	26 (3)	33 (3.9)	27 (3.2)	26 (3)
	EPO	163	15 (9.2)	8 (4.9)	5 (3.1)	5 (3.1)	10 (6.1)	8 (4.9)	4 (2.5)	3 (1.8)
open-label	ARANESP	1429	188 (13.2)	62 (4.3)	60 (4.2)	48 (3.4)	50 (3.5)	49 (3.4)	41 (2.9)	38 (2.7)
	EPO	265	28 (10.6)	17 (6.4)	8 (3)	8 (3)	14 (5.3)	17 (6.4)	8 (3)	7 (2.6)
blinded	ARANESP	169	22 (13)	13 (7.7)	8 (4.7)	8 (4.7)	4 (2.4)	2 (1.2)	5 (3)	2 (1.2)
	EPO	335	40 (11.9)	22 (6.6)	15 (4.5)	9 (2.7)	18 (5.4)	10 (3)	11 (3.3)	6 (1.8)
correction	ARANESP	348	50 (14.4)	5 (1.4)	13 (3.7)	16 (4.6)	12 (3.4)	5 (1.4)	8 (2.3)	8 (2.3)
	EPO	77	4 (5.2)	3 (3.9)	1 (1.3)	1 (1.3)	3 (3.9)	1 (1.3)	0 (0)	0 (0)
conversion	ARANESP	1250	160 (12.8)	70 (5.6)	55 (4.4)	40 (3.2)	42 (3.4)	46 (3.7)	38 (3)	32 (2.6)
	EPO	523	64 (12.2)	36 (6.9)	22 (4.2)	16 (3.1)	29 (5.5)	26 (5)	19 (3.6)	13 (2.5)
HD	ARANESP	1341	166 (12.4)	73 (5.4)	61 (4.5)	48 (3.6)	46 (3.4)	45 (3.4)	39 (2.9)	31 (2.3)
	EPO	537	63 (11.7)	38 (7.1)	21 (3.9)	16 (3)	30 (5.6)	27 (5)	18 (3.4)	13 (2.4)
PD	ARANESP	128	35 (27.3)	2 (1.6)	3 (2.3)	7 (5.5)	5 (3.9)	3 (2.3)	7 (5.5)	5 (3.9)
	EPO	26	4 (15.4)	0 (0)	1 (3.8)	0 (0)	1 (3.8)	0 (0)	1 (3.8)	0 (0)
pre-dialysis	ARANESP	129	9 (7)	0 (0)	4 (3.1)	1 (0.8)	3 (2.3)	3 (2.3)	0 (0)	4 (3.1)
	EPO	37	1 (2.7)	1 (2.7)	1 (2.7)	1 (2.7)	1 (2.7)	0 (0)	0 (0)	0 (0)

Antibody Results:

The median number of weeks between the first dose of study agent and the last antibody sample was 25 weeks (range 1–115) for ARANESP and 29 weeks (range 2–71) weeks for EPO. One subject in the ARANESP group had a single positive sample at week 24; however, subsequently that subject had negative results at weeks 36 and 38. The significance of the apparent reversion to a negative titer is unknown.

Table 32: Antibody Assay Results

	ARANESP	EPO
Number of Subjects	1598	600
Number of Subjects with Antibody Assay Results	1560	584
Screening Assay		
Seronegative	1559 (99.94%)	584 (100%)
Seropositive	1 (0.06%)	0 (0%)

Severe Adverse Events:

Severe adverse events with a frequency ≥ 1 % in the ARANESP group are summarized in Table 33. The numbers of events were fairly limited, precluding meaningful subgroup analyses. Events with a relative risk (RR) ARANESP:EPO > 2.0 are shown in boldface type. Asterisks indicate events that are generally specific to mode of dialysis, for which the Ns were restricted to particular subgroups (e.g., vascular access complications in the subgroup of subjects receiving HD). With respect to potential differences in safety between ARANESP and EPO, the numbers of events are generally too small to either suggest particular concerns regarding ARANESP, or, on the other hand, to provide meaningful reassurance.

Anaphylaxis and Allergic Reactions:

There were no anaphylactic events reported in these studies. CBER found reports of allergic reactions in 24 ARANESP-treated subjects (1.5%), and 10 EPO-treated subjects (1.7%). These were variously coded as “allergy attack,” “allergic attack,” “itch,” “urticaria,” etc. There was one report of angioedema in an ARANESP subject on Week 42 of treatment. Approximately 1/3 of the reports attributed allergic reactions to a particular drug or event (i.e., vancomycin, chlorhexidine, protamine, iron, heparin, angiography, mosquito bites, etc.). Overall, the pattern does not suggest excess allergic events in ARANESP-treated subjects, or allergy to ARANESP per se.

Table 33: Severe Adverse Events with Incidence [3] 1% in the ARANESP Treatment Group

	ARANESP		EPO	
	N*	events (%)	N*	events (%)
Peritonitis*	**126**	**13 (10.3%)**	**26**	**1 (3.8%)**
Hypertension	1598	51 (3.2%)	600	17 (2.8%)
Thrombosis Vascular Access*	1343	34 (2.5%)	537	20 (3.7%)
Hypotension	1598	32 (2%)	600	13 (2.2%)
Angina/CAD	**1598**	**30 (1.9%)**	**600**	**3 (0.5%)**
Sepsis	1598	29 (1.8%)	600	7 (1.2%)
Pulmonary Edema	1598	26 (1.6%)	600	8 (1.3%)
Cardiac failure	**1598**	**26 (1.6%)**	**600**	**4 (0.7%)**
Dyspnea	1598	23 (1.4%)	600	9 (1.5%)
Chest Pain	1598	23 (1.4%)	600	6 (1%)
Access infection*	1343	23 (1.7%)	537	5 (0.9%)
Myocardial infarction	1598	22 (1.4%)	600	11 (1.8%)
Fever	**1598**	**22 (1.4%)**	**600**	**2 (0.3%)**
Myalgia	1598	21 (1.3%)	600	14 (2.3%)
Pain abdominal	1598	21 (1.3%)	600	9 (1.5%)
Fluid overload	1598	21 (1.3%)	600	5 (0.8%)
GI Hemorrhage	1598	21 (1.3%)	600	5 (0.8%)
Anemia	1598	20 (1.3%)	600	6 (1%)
Pneumonia	1598	19 (1.2%)	600	6 (1%)
Cardiac Arrest	1598	18 (1.1%)	600	9 (1.5%)
Headache	1598	16 (1%)	600	11 (1.8%)
Diarrhea	**1598**	**16 (1%)**	**600**	**1 (0.2%)**
Access Stenosis*	1343	14 (1%)	537	5 (0.9%)

* N adjusted for appropriate mode of dialysis (i.e., HD, PD) subgroup
Events with RR > 2 are shown in bold font

CBER's Exploratory Safety Analyses:

As previously noted, investigations in the ARANESP clinical development program were largely active-controlled or uncontrolled studies, lacking a placebo group, and the vast majority of the experience was open-label. Moreover, analyses of AEs are obfuscated by high background rates of events in the CRF population. CBER took a number of approaches in its assessment of the ARANESP safety database, beyond simple comparisons of AE rates in ARANESP- and EPO-treated subjects and subgroups:

1. Adverse Events by Mean Weekly Weight-Adjusted Dose. Analyses of AEs by mean weekly dose of study agent have the potential to elucidate general dose-related toxicities. The sponsor analyzed the safety database with classification of subjects by mean weekly weight-adjusted dose tertile; however, the analyses were not adequate for reasons noted above (i.e., many AEs were misclassified and some categories were split, leading to substantial underestimation of some AE rates). Moreover, subjects in open-label and blinded studies were reported separately. CBER analyzed the edited AE database, dividing subjects into quintiles based on mean weekly weight-

adjusted dose. Subjects were analyzed by treatment group, and not distinguished by study design (i.e., open-label versus blinded studies).

2. Adverse Events by Weight-Adjusted Dose Quartiles, Dose Received During the 4 Weeks Preceding Event. Analyses of AEs by mean weekly dose fail to take into consideration the dynamics of dose titration, and are insensitive to toxicities due to transient changes in dose. Thus, CBER analyzed AEs by weight-adjusted dose quartiles, on the basis of the total dose of study agent administered during the 4 weeks preceding reported AEs. The selection of 4 weeks was somewhat arbitrary, but the goal was to choose a time frame wherein dose was likely to strongly influence effect.
3. Adverse Events by Weight-Adjusted Dose, Week of Event. CBER performed a similar analysis, based on the weight-adjusted dose of study agent administered during the week of reported AEs.
4. Adverse Events With Putative Mechanisms Involving Hemodynamic and/or Rheologic Factors:
   A) Analysis of AEs by Hgb Concentration. CBER assessed AEs by Hgb concentration as determined on the week of the reported event. This purpose of this analysis was to provide information on potential associations between AEs and specific Hgb levels.
   B) Analysis of AEs by Hgb Rate of Rise. CBER assessed AEs by Hgb rate of rise (ROR) during the weeks preceding reported AEs. The objective of this analysis was to assess potential associations between AEs and specific rates of Hgb increase.
   C) Analysis of AEs by Hgb Rate of Decline. This complementary analysis assessed rates of AEs by Hgb rate of decline during the weeks preceding the events.
   D) Examination of Potential Interaction Between Hgb Concentration, Hgb Rate of Rise and AEs: CBER combined all AEs with putative mechanisms involving hemodynamic and/or rheologic factors, and examined the interaction between the rate of these AEs, Hgb concentration and Hgb ROR.

Relation Between Adverse Events and Dose of Study Agents:

Mean Weekly Weight-Adjusted Dose:

CBER classified subjects into quintiles, based on mean weekly weight-adjusted dose of study agent administered. For ARANESP, quintiles were demarcated at doses of <0.295, <0.421, <0.572, and <0.819 and ≥0.819 μg/kg/week, respectively. For EPO, the corresponding cut-offs were <66.0, <98.6, <141 and <219 and ≥219 units/kg/week. All AEs with a reported frequency of >4% in the ARANESP group, as well as seizures, were categorized by the subject's weekly weight-adjusted dose quintile, and tabulated by treatment group (Table 34, left). (Though the rate of seizures was <4%, they are included in the table, both because of the general concern regarding seizures and erythropoietins, and because rates of seizures were strongly associated with dose.) The numbers listed for specific AEs and quintiles represent raw event numbers (i.e., *not* subject incidences). The order in which AEs are listed is based on the strength of the association between AE frequency and dose. For each AE, the slope of the relation between the numbers of events in each quintile (divided by the total number of events) and the dose quintile was determined (least-squares), and AEs were sorted by decreasing slope. Thus, events at the top of the table have the strongest relation to weekly weight-adjusted dose; events at the bottom of the table show the strongest *negative* association. The gray line is placed at the position of zero-slope (i.e., no relation to dose). Thus, the vast majority of AEs with incidence > 4% are positively associated with dose. It should be pointed out, however, that the existence of an association, per se, does not substantiate cause and effect.

The trends for ARANESP and EPO are generally similar. The association of worsened anemia with mean weekly weight-adjusted dose suggests that the majority of subjects who experienced worsening anemia did so *despite treatment with higher doses of ARANESP*, whereas only a minority of subjects experienced worsening anemia *in association with lower ARANESP doses*. A number of AEs for which there was a positive association have hemodynamic mechanisms as their pathophysiologic basis. In particular, dyspnea/tachypnea, pulmonary edema/congestion, and CHF may be precipitated by excessive Hgb rate of

rise (see below), which could be related to excessive ARANESP dosing. The sole AE with a strongly negative association with weekly ARANESP dose was injection site pain. This suggests, not surprisingly, that subjects who complained of injection site pain were less likely to have their ARANESP doses increased. (For EPO, the frequency of injection site pain was essentially nil.) With respect to other events, however, the similarities in the relations between the ARANESP and EPO groups suggest that the two agents are not fundamentally different with regard to safety.

Weight-Adjusted Dose Administered During the 4 Weeks Preceding AE:

Each study week for each subject was classified into quartiles, based on the total weight-adjusted dose of study agent administered during the prior 4 weeks (i.e., the dosing quartile calculated for week 9 of a given subject was based on cumulative dose administered during weeks 5, 6, 7, and 8). The quartile cut-offs for the ARANESP group were <1.10, <1.81, <2.82 and ≥2.82 μg/kg/4 weeks. For the EPO group, the corresponding cut-offs were <235, <413, <686 and ≥686 units/kg/4 weeks. Each of the 19,272 AEs with a valid recorded start week was cross-referenced with the 62,983 records representing the quartiles for study weeks of all subjects, resulting in ~1.2 billion "look-ups." Adverse events were then tabulated by quartile and by treatment group. AEs with frequency >4%, as well as seizures, are shown (Table 34, right). The numbers listed for specific AEs and quartiles represent raw numbers of events (i.e., not subject incidences). Overall, there are relatively strong, positive relations between frequencies of AEs and weight-adjusted doses of study agents administered within the 4 weeks preceding events. The patterns for the ARANESP-treated group parallel those of the EPO group, and are similar to the relations between frequencies of AEs and mean *weekly* weight-adjusted dose (described above). Notable AEs with strongly positive associations between event frequency and weight-adjusted ARANESP dose administered during the prior 4 weeks include: seizure, worsened anemia, malaise, hemorrhage/hematoma, CHF, pulmonary edema/congestion, dyspnea/tachypnea, TVA, anorexia, fever, and sepsis. The single event with a prominent negative association was injection site pain, as above. Again, the similarity between the relations for ARANESP and EPO suggests that the two products are basically comparable from a safety standpoint. The consistency between treatment groups also suggests that these associations are not chance findings.

Weight-Adjusted Dose Administered at Week of AE:

Each study week of each subject was divided into quartiles, based on the weight-adjusted dose of study agent administered *that week*. For the ARANESP group, the quartile cut-offs were <0.313, <0.471, <0.746 and ≥0.746 μg/kg. For the EPO group, the corresponding cut-offs were <63.8, <110, <180 and ≥180 units/kg. The results were very similar to the results for the weight-adjusted dose administered for the 4 weeks preceding events, and the results are not shown.

Table 34: Relation Between AEs and Dose of Study Agents

	Mean Weekly Weight-Adjusted Dose Quintiles										Total Weight-Adjusted Dose - 4 Weeks Preceding Event - Quartiles							
	ARANESP					EPO					ARANESP				EPO			
Quantile (low --> high)	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
seizure	2	1	5	6	7	0	2	0	3	6	3	6	2	10	0	3	3	5
anemia, worsened	4	12	13	16	23	7	7	4	8	12	10	9	28	21	10	6	6	16
hemorrhage, hematoma	9	19	18	22	36	16	22	26	51	23	14	24	31	35	20	22	50	46
dyspnea; tachypnea	28	26	60	69	75	32	38	21	27	52	44	52	73	88	43	32	32	63
malaise	8	7	23	25	19	10	3	6	14	15	11	15	32	24	9	8	13	18
pulmonary edema; congestion	8	7	11	16	18	7	5	3	6	24	6	19	16	19	8	6	6	25
anorexia	8	10	14	9	23	10	5	5	9	11	12	14	16	22	7	9	6	18
fever, rigors	31	30	32	47	64	14	17	17	15	30	42	41	47	74	21	17	22	33
diarrhea	36	60	51	73	82	22	38	26	44	40	50	83	73	96	26	48	33	63
gastrointestinal bleeding	7	11	12	20	13	3	6	6	10	3	11	17	16	19	8	5	6	9
CHF	15	8	18	22	22	9	4	3	3	17	11	21	24	29	9	5	3	19
TVA	20	28	35	35	43	27	14	24	45	46	27	34	49	51	33	21	44	58
nausea/ vomiting	97	110	108	179	170	67	71	61	88	113	125	185	146	208	87	66	89	158
sepsis, bacteremia	9	5	19	19	12	0	6	1	10	6	12	11	22	19	4	2	9	8
angina, CAD	28	14	46	44	39	17	4	13	7	19	32	43	50	46	15	12	13	20
access complication (excluding infection and TVA)	56	64	104	86	108	46	52	46	100	74	88	92	124	114	61	50	97	110
cough	39	39	48	45	72	17	24	18	17	31	51	54	60	78	27	21	24	35
arthralgia/ arthritis	41	39	44	61	63	19	23	25	25	20	58	47	73	70	23	24	32	33
pain back	19	25	25	24	36	11	16	17	20	19	29	25	45	30	20	17	15	31
abdominal pain	39	37	40	50	60	19	17	21	27	37	57	50	44	75	24	15	28	54
fall	11	8	21	14	16	7	3	7	6	15	8	21	24	17	3	7	9	19
hypotension	114	112	82	139	171	64	88	27	58	80	136	141	139	201	76	87	64	90
access infection	20	20	26	26	31	11	6	7	10	10	30	28	30	35	13	9	11	11
confusion, agitation, anxiety	19	19	6	20	29	7	12	7	13	20	28	20	11	34	10	10	12	27
skin ulceration	15	11	13	16	20	1	8	3	9	3	12	22	21	20	5	5	7	7
asthenia, fatigue	46	35	67	47	66	34	21	19	37	37	59	61	71	70	40	12	39	57
infection	143	166	185	203	213	73	75	77	67	91	203	226	230	251	107	70	89	117
constipation	13	16	18	19	18	9	8	8	14	9	23	22	19	20	11	11	9	17
edema	120	64	83	150	109	44	94	40	77	117	120	106	161	139	44	104	76	148
dizziness	23	28	38	25	33	21	23	20	21	32	31	38	38	40	30	24	27	36
epistaxis	13	5	15	18	10	1	6	1	8	14	19	11	19	12	3	7	6	14
headache	72	70	73	81	82	22	40	25	25	48	93	95	97	93	28	40	38	54
myalgia	111	112	107	117	130	55	69	49	74	62	141	144	132	160	67	73	82	87
pain limb	38	33	30	38	42	18	13	19	23	39	42	37	49	53	20	18	25	49
insomnia, sleep disorder	12	10	10	5	16	7	10	3	6	9	16	14	5	18	5	12	6	12
fluid overload	19	33	27	22	27	10	14	16	9	13	26	36	30	36	9	17	21	15
arrhythmia	31	32	43	38	31	19	26	30	30	29	49	41	44	41	28	29	38	39
impaired consciousness, ataxia, hypertonia, hypoesthesia, paresthesia	37	22	33	37	32	13	22	12	20	34	45	39	34	41	20	23	21	37
hypertension	85	104	117	86	99	27	44	47	52	43	110	124	130	127	38	50	68	57
Zero Slope - No Relation																		
URI, rhinitis	93	82	69	86	88	51	41	49	42	48	115	97	103	103	62	39	63	67
influenza-like symptoms	17	25	15	21	18	9	12	19	5	4	25	27	22	22	16	12	16	5
pruritus	31	28	24	38	21	3	15	11	7	9	47	28	39	28	8	15	11	11
injection site pain	35	41	35	25	14	0	2	2	0	0	86	36	18	10	3	0	1	0

Relation Between Serum Hgb and Adverse Events With Putative Mechanisms Involving Hemodynamic and/or Rheologic Factors:

Absolute Hgb concentration and the rate of rise of Hgb concentration may be associated with extravascular volume expansion and increased hemodynamic stress, as well as augmented blood viscosity. These factors may be lead to excess risk of cardiovascular events including accelerated HTN, volume overload, CHF, pulmonary edema, thrombosis, TVA, acute myocardial infarction/ischemia, peripheral infarction/ischemia, stroke, TIA and seizures. These relations have complex interactions, however, and the ideal Hgb target range remains somewhat controversial. For example, poorly controlled anemia with impaired oxygen-carrying capacity may lead to myocardial ischemia/infarction, whereas the same events may be precipitated by overly-rapid erythropoiesis with volume overload, accelerated HTN, and increased blood viscosity.

When Epoetin alfa was initially approved, a target HCT range of 30 – 33% (maximum 36%) was recommended for anemia of CRF. (This would correspond to Hgb range of roughly 10 – 11 g/dL, maximum 12 g/dL). In 1994, FDA permitted simplification and liberalization of the target HCT range to 30 – 36%.

Amgen subsequently sponsored an investigation (the "Normal Hematocrit Study") to evaluate the potential risks and benefits of normalizing the HCT in HD patients with cardiac disease (CHF or ischemic heart disease).[2] Patients were randomized to receive increasing doses of EPO to achieve and maintain a HCT of 42±3%, or to continue to receive EPO to maintain HCT at 30±3%. The primary end point was the time to death or non-fatal MI. The study was halted for futility when there was a strong trend in favor of *higher* rates of mortality and non-fatal MI in the *normal* HCT group (risk ratio for the normal:low HCT groups: 1.3; 95% CI, 0.9 to 1.9). The incidences of non-fatal MI were 3.1% and 2.3% in the normal and low HCT groups, respectively. The incidences of TVA (39% versus 29%) and all other thrombotic events (22% versus 18%) were also higher in the normal HCT group. Paradoxically, however, mortality rates *decreased* with *increasing HCT* values within both groups. The results of this study underscored the risk of overly-aggressive use of erythropoietins and resulted in a the addition of a Warning in the EPO Package Insert; however, the study left in doubt the optimal target HCT range. The inconsistency of the results also suggested a disconnect between Hgb rate of rise and Hgb concentration, per se. Specifically, a plausible interpretation of the results is that a higher Hgb generally conveys benefit; however, this is countered by inherent risks associated with the act of raising Hgb. Whether that risk is related specifically to EPO, or to its pharmacodynamic effects, is unclear.

In light of these uncertainties, CBER assessed possible relations between AEs with putative mechanisms involving hemodynamic/ rheologic factors and serum Hgb concentration, as well as potential associations between these events and the Hgb ROR. The goals were to characterize AEs by the Hgb value reported on the week of the event, as well as by the slope of the Hgb-time relation *leading up to the week of the event.*

Weekly Hgb values were classified by both 1-g/dL range and quintile. Ranges were defined as: ≤10 g/dL, >10 to ≤11 g/dL, >11 to ≤12 g/dL, >12 to ≤13 g/dL, >13 to ≤14 g/dL, and >14 g/dL. Quintiles were ascertained as: <10.1 g/dL, ≥10.1 to <10.8 g/dL, ≥10.8 to <11.4 g/dL, ≥11.4 to <12.2 g/dL, and ≥12.2 g/dL.

For each subject-week, the slope of the preceding Hgb-time relation was determined, when possible, using the following approach:

[2] Besarab A, et al. N Engl J Med 1998;339:584

1. The slope of the Hgb-time relation leading up to each date was calculated using Hgb values obtained over a 2-week period (i.e., 3 Hgb values).
2. Missing Hgb values were not interpolated.
3. Hgb values were construed as having been obtained on the week indicated, i.e., the actual date was not used in calculations. Slopes were expressed as weekly change in Hgb concentration.
4. If <2 Hgb values were reported over a 2-week (3-value) period, such that a slope could not be calculated, an attempt was made to calculate slope over a 4-week period.
5. Positive and negative slopes were analyzed separately, with slopes of 0 classified with the positive slopes.
6. Slope (m) was classified by group, as follows:
   - $m \leq 0.1$ g/dL/week (≤ 1 g/dL per 10 weeks)
   - $m > 0.1$ and ≤ 0.2 g/dL/week (1 g/dL per <10 to 5 weeks)
   - $m > 0.2$ and ≤ 0.25 g/dL/week (1 g/dL per <5 to 4 weeks)
   - $m > 0.25$ and ≤ 0.333 g/dL/week (1 g/dL per <4 to 3 weeks)
   - $m > 0.333$ and ≤ 0.5 g/dL/week (1 g/dL per <3 to 2 weeks)
   - $m > 0.5$ and ≤ 1 g/dL/week (1 g/dL per < 2 to 1 week)
   - $m > 1$ g/dL/week (1 g/dL per <1 week)

Each AE reported was linked, by reported week of occurrence, to its associated weekly Hgb value range, quintile, and slope. Multiple AEs were linked by pathophysiologic mechanism, e.g., fluid overload included edema, dyspnea, orthopnea and pleural effusion. Congestive heart failure (CHF), abnormal ejection fraction and pulmonary edema were grouped together. Cerebrovascular disorders included cerebral ischemia, ICH, cerebral/subarachnoid hemorrhage. Angina was grouped with coronary artery disease, myocardial ischemia, and chest pain (non-specific chest pain was not included in this category). A category representing thrombosis/ischemia (but omitting TVA) was constructed including the terms arterial occlusion, embolism, arteriosclerosis, carotid stenosis, claudication, peripheral vascular disease, ischemic necrosis, gangrene, superior vena caval syndrome, phlebitis, thrombophlebitis, arterial/venous thrombosis, intestinal ischemia, pulmonary embolism, and TIA.

Absolute Hgb Values (Table 35):

Serum Hgb was analyzed both by quintiles, and by 1-gram/dL categories. For each quintile and category, the denominator used was the number of weekly Hgb values observed that fit that particular category, divided by 1000 (i.e., the number of events per 1000 weekly Hgb observations). The Ns are given at the bottom of Table 35.

For ARANESP-treated subjects, there were trends suggesting possible associations between reported Hgb values > 13 and seizures, HTN, and arrhythmias, though the latter appeared to be associated with Hgb values ≤ 11 g/dL, as well. Importantly, Hgb values of ≤ 13 g/dL did not appear to be associated with increased risks of these events. Of note, for ARANESP-treated subjects, Hgb values ≤ 10 g/dL appeared to be associated with excess risks of fluid overload, CHF, pulmonary edema, acute MI and TVA, whereas these risks were not apparent at Hgb values > 10 g/dL.

Table 35: CBER Analysis of Relation Between Serum Hgb and AEs With Putative Mechanism Involving Hemodynamic and/or Rheologic Factors: Combined Data (Rates are Events /1000 weekly Hgb Observations)

		Hgb	Hgb Category (g/dL)					
		unknown	<10	10 to <11	11 to <12	12 to <13	13 to <14	14 +
polycythemia	EPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	ARANESP	0.0	0.0	0.0	0.0	0.0	0.4	7.2
	Total	0.0	0.0	0.0	0.0	0.0	0.3	5.2
hypertension	EPO	8.5	9.3	11.2	11.6	10.4	10.5	12.2
	ARANESP	5.5	12.1	12.0	11.0	11.0	15.6	9.6
	Total	6.0	11.3	11.7	11.2	10.8	14.2	10.4
fluid overload: edema, dyspnea, orthopnea, pleural effusion	EPO	19.1	27.9	21.1	22.9	24.9	12.9	12.2
	ARANESP	9.4	26.5	16.3	11.9	12.1	12.2	7.2
	Total	11.1	26.9	17.8	15.5	15.9	12.4	8.6
CHF, abnormal ejection fraction, pulmonary edema	EPO	0.7	4.5	2.3	1.1	1.0	1.2	0.0
	ARANESP	1.5	4.4	1.7	1.0	0.6	0.8	4.8
	Total	1.4	4.4	1.9	1.0	0.7	0.9	3.5
cerebrovascular disorder, cerebral ischemia, ICH, cerebral hemorrhage, SAH	EPO	0.0	0.3	0.8	0.4	0.7	0.0	0.0
	ARANESP	0.3	0.7	0.8	0.3	0.3	0.8	0.0
	Total	0.3	0.6	0.8	0.3	0.4	0.6	0.0
impaired consciousness, encephalopathy	EPO	0.0	1.8	0.8	0.5	1.7	0.0	0.0
	ARANESP	0.0	0.4	0.8	0.1	0.4	0.0	0.0
	Total	0.0	0.8	0.8	0.2	0.8	0.0	0.0
seizure	EPO	1.1	0.6	0.4	0.4	1.0	0.0	0.0
	ARANESP	0.3	0.6	0.5	0.5	0.3	0.8	4.8
	Total	0.4	0.6	0.4	0.5	0.5	0.6	3.5
syncope	EPO	0.7	0.9	1.2	1.1	1.7	0.0	0.0
	ARANESP	0.9	0.8	1.0	0.5	1.5	0.4	0.0
	Total	0.9	0.8	1.0	0.7	1.5	0.3	0.0
acute MI	EPO	0.7	0.9	0.8	0.4	0.3	0.0	0.0
	ARANESP	0.5	1.0	0.5	0.2	0.4	0.4	0.0
	Total	0.5	1.0	0.6	0.2	0.4	0.3	0.0
cardiac arrest	EPO	0.0	0.6	0.0	0.5	0.7	1.2	6.1
	ARANESP	0.2	0.6	0.3	0.2	0.0	0.4	0.0
	Total	0.2	0.6	0.2	0.3	0.2	0.6	1.7
arrhythmia	EPO	6.6	5.4	7.5	6.4	9.0	8.2	0.0
	ARANESP	3.7	4.9	4.9	2.6	3.1	7.6	7.2
	Total	4.2	5.1	5.7	3.9	4.8	7.7	5.2
death	EPO	0.4	0.0	0.0	0.2	0.0	0.0	0.0
	ARANESP	0.2	0.2	0.2	0.0	0.0	0.0	0.0
	Total	0.2	0.2	0.1	0.1	0.0	0.0	0.0
angina, CAD, myocardial ischemia, pain chest	EPO	2.6	4.5	4.4	2.1	2.1	0.0	12.2
	ARANESP	3.9	4.8	3.4	2.9	4.4	2.9	4.8
	Total	3.6	4.7	3.7	2.7	3.7	2.2	6.9
arterial occlusion, arteriosclerosis, carotid stenosis, claudication, gangrene, ischemic necrosis, peripheral ischemia, arterial embolism, phlebitis, thrombophlebitis, SVC syndrome, arterial thrombosis, venous thrombosis, intestinal ischemia, TIA, pulmonary embolism	EPO	1.8	4.8	2.3	1.3	2.4	1.2	12.2
	ARANESP	2.4	3.6	2.3	1.7	3.2	2.1	2.4
	Total	2.3	3.9	2.3	1.5	3.0	1.9	5.2
TVA	EPO	3.7	9.3	6.6	7.7	8.6	3.5	12.2
	ARANESP	1.6	5.1	3.2	3.9	3.5	2.5	0.0
	Total	2.0	6.3	4.3	5.1	5.0	2.8	3.5
anemia	EPO	1.5	8.7	0.8	0.0	0.0	0.0	0.0
	ARANESP	0.5	6.0	0.6	0.1	0.1	0.0	0.0
	Total	0.7	6.8	0.7	0.1	0.1	0.0	0.0
hypovolemia, hypotension, postural hypotension, dehydration	EPO	12.9	17.7	13.9	17.2	18.3	16.4	12.2
	ARANESP	9.2	11.2	15.4	16.1	14.7	18.5	9.6
	Total	9.8	13.0	14.9	16.4	15.8	18.0	10.4
Number of values (N)	**EPO**	2716	3329	5178	5585	2894	856	164
	ARANESP	12925	8937	11013	11395	6878	2373	415
	Total	15641	12266	16191	16980	9772	3229	579

Overall, these data suggest an optimum safe Hgb range of > 10 to £ 13 g/dL for ARANESP-treated subjects in these studies. ***Given the frequency with which out of range Hgb values were encountered in these studies, however, the Hgb target should encompass a subset of values that lie well within the ideal range.***

Hgb Rate of Rise (Table 36):

Adverse events are shown for Hgb rates of rise and fall in Table 36. Rates were determined by whole fractions of a gram of Hgb (i.e., 1.0, 0.5, 0.33, 0.25, 0.20, and 0.10 g/dL/week). The denominators used for each quintile and category were the number of weekly Hgb slopes that fit that particular category, divided by 1000 (i.e., the number of events per 1000 weekly Hgb observations, table bottom).

The number of Hgb observations in the > 1-gram/dL per week slope categories was limited, such that the event rates are of questionable informativeness.

For ARANESP-treated subjects, there appears to be excess risk of HTN, pulmonary edema, cardiac arrest and TVA associated with Hgb ROR >0.5 and particularly 1.0 g/dL/week. There also appears to be an association between rapid Hgb rise and fluid overload, acute MI and seizures, although the association between Hgb rate of rise and these events is less clear. These findings should be included in labeling.

CBER also assessed the rates of these AEs in the ARANESP treatment group, with subgroups by history of cardiovascular disease (CVD). Across Hgb and Hgb ROR categories, event rates generally followed similar patterns for subjects with and without a history of CVD, though rates were higher in CVD(+) subjects. There were 2 apparent exceptions:

1) CHF was strongly associated with the extremes of Hgb categories (both <10 and >14 g/dL) in the CVD(+) group, whereas there was only a weak association between CHF and Hgb <10 g/dL in the CVD(-) subgroup. A Hgb ROR exceeding 0.5 was strongly associated with CHF, both in CVD(+) and CVD(-) subgroups.
2) There was no clear association between angina and Hgb ROR in either subgroup; however, a Hgb <10g/dL was strongly associated with angina in the CVD(+) group.

Hgb Rate of Decline:

With respect to falling Hgb in ARANESP-treated subjects (rate of Hgb decrease preceding AEs), there were apparent associations between a >1 g/dL weekly decline in Hgb and worsened anemia, CHF, pulmonary edema, acute MI, cardiac arrest, angina, arterial occlusion, and death, though the numbers of subject-weeks and events in this category were limited.

Interaction Between Hgb Concentration, Hgb Rate of Rise, and AEs:

For the ARANESP treatment group, CBER combined AEs with putative mechanisms involving hemodynamic and/or rheologic factors, and examined the interaction between the rate of these AEs, Hgb concentration and Hgb ROR. These events included: accelerated HTN, fluid overload, edema, dyspnea, orthopnea, pleural effusion, pulmonary edema, CHF, abnormal ejection fraction, angina, coronary artery disease, myocardial ischemia, chest pain (cardiac), arrhythmia, syncope, cardiac arrest, impaired consciousness, encephalopathy, seizure, cerebrovascular disorder, TIA, cerebral ischemia, ICH, subarachnoid hemorrhage, arterial occlusion, arteriosclerosis, carotid stenosis, claudication, gangrene, ischemic necrosis, peripheral ischemia, arterial embolism, phlebitis, superior vena caval syndrome, thrombophlebitis, arterial/venous thrombosis, and intestinal ischemia. Each AE was linked, by week of reported occurrence, to its corresponding Hgb category, as well as to its appropriate Hgb ROR category.

Table 36: CBER Analyses of Relations Between Hgb ROR and Rate of Fall and AEs With Putative Mechanism Involving Hemodynamic and/or Rheologic Factors: Combined Data (Events/1000 weekly Hgb observations)

		Rate of Rise (g/dL/week)							Rate of Fall (g/dL/week)						
		≤0.1	>0.1 to ≤0.2	>0.2 to <0.25	>0.25 to ≤0.33	>0.33 to <0.5	>0.5 to <1	>1	≤0.1	>0.1 to <0.2	>0.2 to <0.25	>0.25 to ≤0.33	>0.33 to <0.5	>0.5 to <1	>1
polycythemia	EPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	ARANESP	0.1	0.0	0.0	0.0	0.5	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.1	0.0	0.0	0.0	0.3	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
hypertension	EPO	11.4	8.8	8.8	11.9	11.3	15.7	21.1	11.2	9.8	6.8	10.4	7.5	16.3	4.6
	ARANESP	7.5	9.9	10.4	13.8	10.2	19.9	13.1	12.0	11.5	14.9	9.6	11.5	10.5	12.4
	Total	8.6	9.5	9.9	13.3	10.6	18.7	15.2	11.7	10.9	12.3	9.8	10.2	12.2	10.2
fluid overload: edema, dyspnea, orthopnea, pleural effusion	EPO	23.0	23.9	10.1	26.4	24.3	19.3	31.6	24.6	26.1	46.4	20.8	23.8	16.3	36.5
	ARANESP	15.4	14.7	16.6	14.4	15.6	18.9	35.4	16.7	21.7	17.4	12.1	17.7	17.3	19.5
	Total	17.6	17.5	14.7	17.8	18.2	19.0	34.4	19.2	23.1	26.7	14.7	19.6	17.0	24.3
CHF, abnormal ejection fraction, pulmonary edema	EPO	2.4	1.0	1.3	1.3	3.2	1.8	0.0	1.3	1.6	1.4	1.5	1.3	6.1	4.6
	ARANESP	1.5	1.5	2.1	2.1	1.4	3.1	7.5	1.6	1.0	3.9	1.3	2.1	4.6	8.9
	Total	1.7	1.4	1.8	1.9	1.9	2.8	5.5	1.5	1.2	3.1	1.3	1.8	5.1	7.7
cerebrovascular disorder, cerebral ischemia, ICH, cerebral hemorrhage, SAH	EPO	0.3	0.5	0.0	0.0	0.0	0.9	0.0	0.9	0.5	0.0	0.0	1.9	0.0	0.0
	ARANESP	0.1	0.4	0.5	0.0	0.5	1.0	1.9	0.6	1.0	0.0	1.3	0.3	0.8	0.0
	Total	0.2	0.5	0.4	0.0	0.3	1.0	1.4	0.7	0.9	0.0	0.9	0.8	0.6	0.0
impaired consciousness, encephalopathy	EPO	1.1	0.0	0.0	1.3	0.5	1.8	0.0	0.9	0.5	0.0	1.5	1.9	2.0	0.0
	ARANESP	0.1	0.7	0.5	0.0	0.2	0.3	0.0	0.4	0.2	0.0	0.0	0.9	1.3	0.0
	Total	0.4	0.5	0.4	0.4	0.3	0.8	0.0	0.6	0.3	0.0	0.4	1.2	1.5	0.0
seizure	EPO	0.3	1.0	0.0	1.3	0.0	0.9	0.0	0.9	0.0	0.0	0.0	0.0	3.0	0.0
	ARANESP	0.4	0.4	0.5	0.5	0.2	1.0	1.9	0.4	0.7	0.0	0.0	0.3	0.4	1.8
	Total	0.4	0.6	0.4	0.8	0.2	1.0	1.4	0.6	0.5	0.0	0.0	0.2	1.2	1.3
syncope	EPO	0.5	1.0	1.3	2.6	0.0	0.0	5.3	1.7	1.6	4.1	1.5	0.6	0.0	0.0
	ARANESP	1.3	0.9	1.0	1.1	0.7	1.4	0.0	1.0	0.7	0.0	0.0	0.0	0.0	3.5
	Total	1.1	0.9	1.1	1.5	0.5	1.0	1.4	1.3	1.0	1.3	0.4	0.2	0.0	2.6
acute MI	EPO	0.8	0.0	0.0	1.3	0.5	0.0	0.0	0.0	1.1	0.0	1.5	1.3	1.0	0.0
	ARANESP	0.4	0.0	1.0	0.0	0.5	0.3	1.9	0.4	1.0	0.0	0.0	0.3	1.7	1.8
	Total	0.5	0.0	0.7	0.4	0.5	0.3	1.4	0.3	1.0	0.0	0.4	0.6	1.5	1.3
cardiac arrest	EPO	0.0	1.0	0.0	0.0	0.5	2.8	0.0	0.4	0.5	0.0	0.0	0.0	1.0	0.0
	ARANESP	0.0	0.2	0.0	0.0	0.0	1.0	1.9	0.0	0.0	0.0	0.0	0.3	2.1	0.0
	Total	0.0	0.5	0.0	0.0	0.2	1.5	1.4	0.1	0.2	0.0	0.0	0.2	1.8	0.0
arrhythmia	EPO	8.5	7.3	5.0	2.6	7.0	2.8	10.5	8.2	5.4	5.5	4.5	9.4	7.1	13.7
	ARANESP	4.5	3.9	4.2	3.2	4.2	4.9	3.7	4.1	3.2	3.2	3.8	3.8	5.9	5.3
	Total	5.6	5.0	4.4	3.0	5.0	4.3	5.5	5.4	3.9	3.9	4.0	5.6	6.3	7.7
death	EPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0
	ARANESP	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.6	0.0	0.0	0.4	3.5
	Total	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.6	2.6
angina, CAD, myocardial ischemia, pain chest	EPO	3.2	1.5	2.5	4.0	2.7	4.6	0.0	0.4	1.6	4.1	3.0	6.9	9.1	9.1
	ARANESP	3.4	4.6	4.7	2.7	3.9	1.7	5.6	3.7	3.7	2.6	5.1	5.0	5.1	8.9
	Total	3.3	3.6	4.0	3.0	3.6	2.5	4.1	2.6	3.1	3.1	4.5	5.6	6.3	8.9
arterial occlusion, arteriosclerosis, carotid stenosis, claudication, gangrene, ischemic necrosis, peripheral ischemia, arterial embolism, phlebitis, thrombophlebitis, SVC syndrome, arterial thrombosis, venous thrombosis, intestinal ischemia, TIA, pulmonary embolism	EPO	1.1	1.9	2.5	4.0	2.2	2.8	5.3	3.0	2.7	0.0	3.0	5.6	5.1	4.6
	ARANESP	1.7	2.6	2.1	4.8	2.1	3.8	7.5	3.1	1.7	1.3	1.3	3.8	3.8	7.1
	Total	1.5	2.4	2.2	4.5	2.1	3.5	6.9	3.1	2.0	0.9	1.8	4.4	4.2	6.4
TVA	EPO	6.1	3.9	5.0	5.3	9.7	15.7	10.5	6.9	6.0	8.2	1.5	5.6	15.2	45.7
	ARANESP	2.6	3.7	2.6	5.3	5.8	5.6	3.7	2.3	3.0	3.2	3.8	4.7	3.8	3.5
	Total	3.6	3.8	3.3	5.3	7.0	8.4	5.5	3.8	3.9	4.8	3.1	5.0	7.1	15.3
anemia	EPO	0.5	0.5	1.3	1.3	0.5	0.0	0.0	0.4	1.6	1.4	1.5	1.3	15.2	32.0
	ARANESP	0.5	0.2	0.0	0.0	0.2	1.0	3.7	0.6	1.7	0.6	3.2	2.7	2.9	28.4
	Total	0.5	0.3	0.4	0.4	0.3	0.8	2.8	0.6	1.7	0.9	2.7	2.2	6.5	29.4
hypovolemia, hypotension, postural hypotension, dehydration	EPO	13.5	19.0	10.1	14.5	18.4	24.9	26.3	13.8	14.7	23.2	17.9	20.0	15.2	22.8
	ARANESP	14.6	11.8	18.2	17.6	17.2	17.1	16.8	16.5	12.7	18.7	6.4	10.9	12.2	12.4
	Total	14.3	14.1	15.8	16.7	17.5	19.2	19.3	15.6	13.3	20.2	9.8	13.8	13.1	15.3
Number of values (N)	**EPO**	3777	2052	796	759	1851	1086	190	2319	1837	733	672	1597	984	219
	ARANESP	9408	4561	1924	1879	4305	2863	536	4852	4017	1548	1568	3395	2376	564
	Total	13185	6613	2720	2638	6156	3949	726	7171	5854	2281	2240	4992	3360	783

The results of this analysis are shown for the ARANESP treatment group in Table 37. The top panel shows the numbers of subject-weeks that fulfill the criteria for Hgb and Hgb ROR categories. These data serve as the denominators (Ns) for these analyses. The middle panel shows the numbers of events for each Hgb/Hgb ROR category, and the bottom panel shows event rates per 1000 subject-weeks. Each row, representing a particular Hgb ROR category, is summed in the right-most column ("All Hgb"). Note that event rates tend to be similar for all ROR categories ≤ 0.50 g/dL/week, whereas event rates for ROR > 0.50 g/dL/week tend to be higher. The individual Hgb categories are summed in the bottom row ("All Slopes"). The lowest event rate is observed in the >11 to ≤12 g/dL Hgb category. A slight increase in event rate is evident above this range, with a sharper increase in event rate below this range.

Table 37: Interaction Between Hgb Concentration, Hgb Rate of Rise, and AEs – ARANESP Group

	N = # Subject-Weeks Fitting Criteria (Denominator)							
	Hgb Category (g/dL) ®	**≤10**	**>10 to ≤11**	**>11 to ≤12**	**>12 to ≤13**	**>13 to ≤14**	**>14**	**All Hgb**
Slope (g/dL/week)	**≤0.1**	1090	1857	1873	1127	374	36	6357
	>0.10 to ≤0.20	536	965	1149	716	245	37	3648
	>0.20 to ≤0.25	237	376	482	359	128	19	1601
	>0.25 to ≤0.33	191	309	441	323	123	28	1415
	>0.33 to ≤0.50	390	735	1009	782	321	71	3308
	>0.50	269	411	593	522	303	129	2227
	All Slopes	2713	4653	5547	3829	1494	320	**18556**

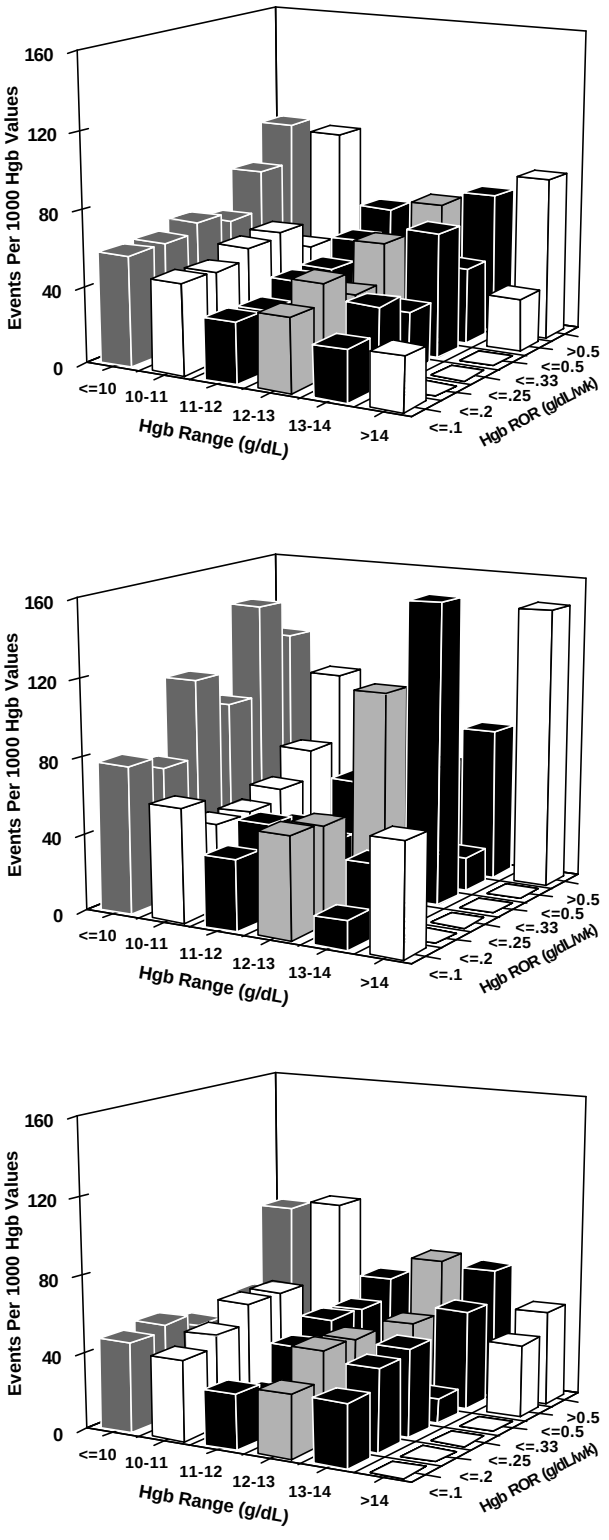
	Numbers of Events							
	Hgb Category (g/dL) ®	**≤10**	**>10 to ≤11**	**>11 to ≤12**	**>12 to ≤13**	**>13 to ≤14**	**>14**	**All Hgb**
Slope (g/dL/week)	**≤0.1**	66	97	65	44	11	1	284
	>0.10 to ≤0.20	32	50	36	38	10	0	166
	>0.20 to ≤0.25	16	20	19	14	4	0	73
	>0.25 to ≤0.33	11	18	17	19	8	0	73
	>0.33 to ≤0.50	33	31	49	32	14	2	161
	>0.50	27	41	36	36	23	12	175
	All Slopes	185	257	222	183	70	15	**932**

	Event Rates Per 1000 Subject-Weeks							
	Hgb Category (g/dL) ®	**≤10**	**>10 to ≤11**	**>11 to ≤12**	**>12 to ≤13**	**>13 to ≤14**	**>14**	**All Hgb**
Slope (g/dL/week)	**≤0.1**	61	52	35	39	29	28	**45**
	>0.10 to ≤0.20	60	52	31	53	41	0	**46**
	>0.20 to ≤0.25	68	53	39	39	31	0	**46**
	>0.25 to ≤0.33	58	58	39	59	65	0	**52**
	>0.33 to ≤0.50	85	42	49	41	44	28	**49**
	>0.50	100	100	61	69	76	93	**79**
	All Slopes	**68**	**55**	**40**	**48**	**47**	**47**	**50**

Figure 17 (top) displays these event rates graphically. A general trend towards higher event rates for the lowest Hgb categories (≤10; >10 to ≤11) is apparent. Moreover, higher event rates of are apparent in the row corresponding to a Hgb ROR >0.5 g/dL/week. The middle panel of Figure 17 shows the event rates for subjects with a history of cardiovascular disease. Rates are generally higher for this subgroup. Of note, higher event rates appear to be associated with the lowest Hgb class (≤10 g/dL), and the highest ROR class (>0.5 g/dL/week). For subjects without a history of cardiovascular disease (lower panel), the events rates tend to be lower, but the trends are similar. Importantly, therefore, even subjects without overt cardiovascular disease appear to incur excess risk with Hgb ROR in excess of 0.5 g/dL/week.

In summary, these analyses do not suggest that higher Hgb concentrations, per se, are associated with increased risk of events that involve hemodynamic or rheologic mechanisms. On the contrary, there is a trend towards higher event rates at the lower end of the Hgb range. Importantly, however, a Hgb ROR >0.5 g/dL/week appears to be associated with increased event rates, irrespective of the presence or absence of overt cardiovascular disease.

Figure 17: Relations Between Hgb, Hgb ROR, and AEs With Hemodynamic/Rheologic Mechanisms – ARANESP Group. Top panel – all subjects; middle panel CVD(+) subjects; bottom panel CVD(-) subjects



Summary and Conclusions:

The data submitted in this application generally support the efficacy and safety of ARANESP for the treatment of anemia associated with CRF. Two studies (Studies 211 and 202) are the active-control studies that constitute the core of efficacy and safety evidence for the CRF indication, for only these studies assess the performance of ARANESP in subjects with anemia. The balance of the data submitted in this application were obtained in the context of *maintenance* of erythropoiesis in subjects who had previously been receiving other recombinant erythropoietins, and should be construed primarily as safety data.

Efficacy:

Though the data are to some extent limited, they provide reasonable evidence of the efficacy of ARANESP in supporting erythropoiesis in CRF patients with anemia. The data do not suggest that ARANESP and EPO are intrinsically different with regard to efficacy. The data do raise the following concerns:

Starting Dose:

It is clear that the original, fixed, dose proportionality for substitution of ARANESP for EPO (i.e., 1 μg ARANESP per 200 Units EPO) has limited utility, because the relation between the agents is non-linear. As a

function of prior EPO dose, ARANESP dose requirements tended to decrease with increasing baseline EPO doses, and ARANESP dose requirements tended to be lower for IV administration than for SC administration. The sponsor calculated ARANESP dose proportionalities based on previous EPO dose that would be of value to include in the Package Insert.

Pre-Dialysis Patients:

ARANESP dosing requirements were lower for pre-dialysis subjects, and the starting dose recommended for dialysis patients may be excessive for pre-dialysis patients. This advice, in some form, is appropriate for labeling.

Overshoot of the Hemoglobin Response:

Overshoot and instability of the Hgb response was observed frequently in these studies. Thus, despite careful monitoring under the auspices of a clinical trial, over one-third of patients who achieved the lower limit of the Hgb target range overshot the range, experiencing Hgb concentrations in excess of 13 g/dL. This was true, both for patients who had had ARANESP initiated de novo for anemia, and for patients who had been previously maintained on EPO. For pre-dialysis patients, and even greater fraction of subjects (roughly two-thirds) exceeded the upper limit of the Hgb target range (13 g/dL). In a safety extension study in which patients had been previously titrated with ARANESP in other studies and had a stable regimen at enrollment, over one-fifth of subjects experienced Hgb concentrations in excess of 13 g/dL. Presumably, in clinical practice wherein monitoring would be expected to be less judicious, overshoot may be more frequent or more pronounced. Thus, the need for careful monitoring can not be over-emphasized, particularly in pre-dialysis patients.

Discontinuation of ARANESP for Hemoglobin in Excess of 14 g/dL:

For subjects who reached a Hgb concentration in excess of 14 g/dL, the median time required for Hgb to decline to <12 g/dL following discontinuation of study agent was 6 – 8 weeks, with a rate of Hgb decease of approximately one-third gram/dL per week. The longer half-life of ARANESP, relative to EPO, has no effect on the rate of Hgb decrease after withdrawal, in that RBC kinetics, and not ARANESP pharmacokinetics, are the determining factor.

Special Patient Populations:

The ARANESP clinical experience for peritoneal dialysis patients, and particularly for patients of African origin, is limited. Registry data indicate that 32% of U.S. CRF patients are of African descent, whereas the number of such subjects in the ARANESP database (11%) is very limited. The pediatric pharmacokinetic data submitted were extremely limited, and inadequate to support pediatric labeling.

Immunogenicity:

---------- antibody assays were performed on sera from 1560 patients. A reactive sample was detected in one patient, though this was thought to be spurious because subsequent samples from that patient were non-reactive. The sensitivity of the sponsor's assay system has not been established, however, and the extent to which subjects may have developed lower antibody titers is uncertain.

General Safety:

Characterization of the safety of ARANESP in this license application was not straightforward, because the substantive investigations were either active-controlled or uncontrolled studies, and

the vast majority of the experience was unblinded. The more subjective Adverse Events were likely to be influenced by both subject and investigator biases. Moreover, Adverse Events occur frequently in the CRF patient population, and Adverse Events attributable to study agents were assessed against this background. Cardiovascular events, in particular, occur commonly in the CRF patient population, yet they also constitute a primary manifestation of excessive erythropoiesis. That being said, the safety of ARANESP appears comparable to that of EPO, though the numbers of events were generally too small to either suggest particular concerns regarding ARANESP, or, on the other hand, to provide meaningful reassurance.

Exploratory analyses suggested that higher Hgb concentration, per se, is not strongly associated with increased rates of events that involve hemodynamic or rheologic mechanisms. Importantly, however, the rate of rise of hemoglobin appears to be particularly relevant with respect to these events. Specifically, a hemoglobin rate of rise in excess of 0.5 g/dL/week appears to be associated with increased event rates, irrespective of the presence or absence of overt cardiovascular disease.

Issues for Phase 4:

Registry data indicate that 32% of U.S. CRF patients are of African descent. The number of such subjects in the database (n = 172) was very limited, partially because of the randomization error in Study 117. For subjects of African descent, hypertension was reported as an AE in 34% of subjects in the ARANESP group, 24% of subjects in the EPO group, raising the possibility of enhanced susceptibility to ARANESP-induced hypertension in patients of African descent. This question, and the safety of ARANESP in patients of African descent, might be addressed in Phase 4 studies.

The pediatric pharmacokinetic data are not adequate to support labeling statements regarding pediatric use of ARANESP, and the final study report for protocol 980212 should be submitted, when available. The ---------- pediatric ---------- and not submitted in the BLA, should be completed as a phase 4 commitment.